The New England
Journal of Medicine

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Volume 251 NOVEMBER 25, 1954 Number 22

CLINICAL USE OF A NOMOGRAM TO ESTIMATE PROPER VENTILATION DURING ARTIFICIAL RESPIRATION*

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WHEN a patient is unable to breathe by himself, the single most important responsibility of the physician is to provide adequate ventilation of the lungs. Artificial respiration during anesthesia may be required for several hours, and the treatment of respiratory paralysis in poliomyelitis may be necessary for much longer periods. Under these conditions the physician must consider any deviations from proper ventilatory levels in the light of their long-term effects.

The first concern of the physician giving artificial respiration is to maintain oxygenation of the patient's arterial blood. Often, he does this by providing high concentrations of oxygen in the inspired air, and as a result oxygen saturation is adequate even at very low levels of ventilation. During short periods of artificial respiration (less than half an hour) meeting oxygen requirements is the most important consideration. When artificial respiration is carried on for longer periods, however, removal of carbon dioxide becomes as important as oxygen supply and can be accomplished only by adequate exchange of gas between the alveoli and the inspired air— that is, by ventilation of the lungs. In general, when artificial respiration is given for long periods, ventilation should be regulated according to the amount of carbon dioxide to be removed.[1] Oxygen therapy should be used when hypoxia persists in spite of adequate ventilation, as in heart disease, anemia, atelectasis or pulmonary edema. In this paper adequacy of ventilation is considered only in relation to arterial carbon dioxide levels, since under most conditions arterial oxygen saturation will be satisfactory when ventilatory removal of carbon dioxide is also satisfactory.

It is not generally appreciated how sensitive the arterial carbon dioxide pressure (pCO_2) is to slight changes in lung ventilation. A sustained decrease in ventilation by only 20 per cent may cause a rise in arterial pCO_2 from 39 to 60 mm. of mercury, whereas a sustained increase in ventilation of 20 per cent may cause the pCO_2 to fall below 30 mm. The fact that, under a wide range of conditions, all normal people at sea level maintain an arterial pCO_2 very close to 39 mm. of mercury illustrates how accurately normal respiration is controlled to meet changing conditions of carbon dioxide production. During prolonged artificial respiration, slight deviations of the pCO_2 from normal are not serious, but if ventilation is greatly decreased, respiratory acidosis and carbon dioxide narcosis result; if ventilation is excessive, respiratory alkalosis, with changes in buffering systems and oxygen transport, becomes a problem.[2]

In poliomyelitis both hypoventilation and hyperventilation should be avoided from the time a respirator is first used.[1-3] When artificial respiration is given for a week or more renal adjustments may correct the pH toward normal, but abnormal carbon dioxide levels may give rise to difficulties even without pH changes. On the one hand, with hypoventilation, the patient may be hypoxic, with evidence of carbon dioxide intoxication. On the other hand, with chronic hyperventilation, the poliomyelitic patient may be near the point of tetany and, in addition, may have great difficulty in regaining independence from the respirator. Once a low pCO_2 becomes established, the patient's normal ventilatory response to carbon dioxide appears to be altered.[4] As a result such "acclimatized" patients resist attempts to decrease their ventilation, and it is much more difficult to wean them from their mechanical aids if their respiratory-muscle strength is diminished.[5] Some of the convalescent poliomyelitic patients we have studied maintain an arterial pCO_2 of 25 to 30 mm. of mercury when breathing on their own, in spite of minimal respiratory reserve.

Although chronic hyperventilation is an important problem in the treatment of respiratory paralysis in poliomyelitis, it is less important in anesthesia, in which hypoventilation and carbon dioxide retention are the chief dangers. Since most anesthesia is given

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Aided by a grant from the National Foundation for Infantile Paralysis, Incorporated.

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in conjunction with a high percentage of oxygen in the inspired air the anesthesiologist is not likely to see cyanosis, and, as a result, he concludes that ventilation is adequate. Serious carbon dioxide retention occurs under these conditions.[6-11] The problem facing the anesthesiologist during controlled respiration is to keep from adding respiratory acidosis (hypoventilation) to the metabolic acidosis accompanying general anesthetics, particularly ether,[6,12-14] chloroform[15] and possibly to a mild extent other anesthetic agents.

To avoid the complications of hyperventilation and hypoventilation, the physician giving prolonged artificial respiration must have an index of the adequacy of ventilation he is providing. The best methods for determining the ventilatory status of a patient involve measurement of the carbon dioxide pressure in either the arterial blood or the alveolar air; these technics are unfortunately not generally available for routine clinical use. This report deals with a method of estimating the adequacy of artificial respiration by direct measurement of the patient's ventilation. Since, as discussed below, it is relatively easy to obtain repeated measurements of total ventilation in terms of the mean tidal volume and breathing frequency, this method does not require expensive apparatus or laboratory tests. When ventilation has been measured, it can then be compared with standards to determine whether it is adequate. Thus, there are two aspects of the procedure: establishment of ventilation standards, and technics of measuring ventilation to compare with the standards.

Nomogram for Determining Proper Tidal Volume

Figure 1 presents a nomogram from which the tidal volume necessary to give a pCO_2 of 40 mm. of mercury may be obtained at a given breathing frequency for a patient of specified sex and body weight. Details of construction of the nomogram will be presented elsewhere. It is based on the fact that basal carbon dioxide production and respiratory dead space are related to body size and may be estimated from body weight. The relation between body weight and carbon dioxide production has been taken from data published by Benedict and Talbot[15] and Harris and Benedict.[16] A survey of data available on respiratory dead space indicates that the dead-space volume is roughly equal to the body weight in pounds. These two characteristics are all that are required to calculate the ventilation necessary to give a mean alveolar

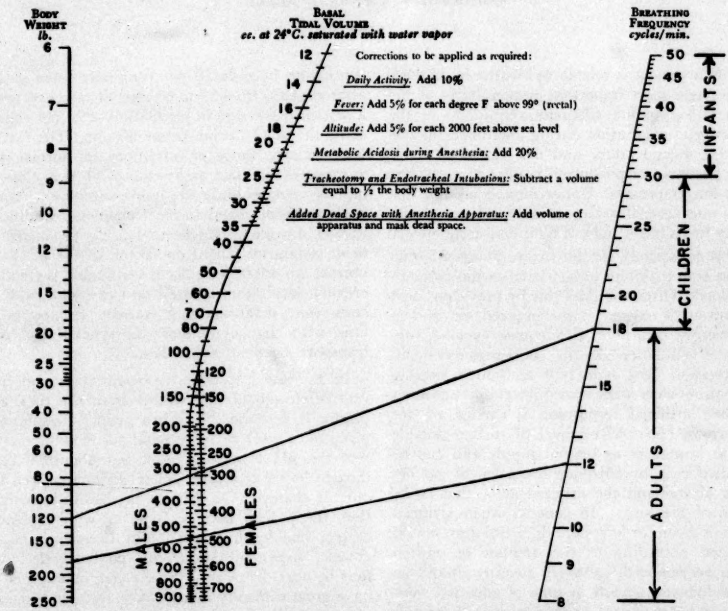
Body Weight lb.
Basal Tidal Volume cc. at 20°C. saturated with water vapor
Breathing Frequency cycles/min.
Corrections to be applied as required:
Daily Activity. Add 10%
Fever: Add 5% for each degree F above 99° (rectal)
Altitude: Add 5% for each 2000 feet above sea level
Metabolic Acidosis during Anesthesia: Add 20%
Tracheotomy and Endotracheal Intubations: Subtract a volume equal to ½ the body weight
Added Dead Space with Anesthesia Apparatus: Add volume of apparatus and mask dead space.
MALES
FEMALES
INFANTS
CHILDREN
ADULTS

FIGURE 1. *Nomogram for Predicting the Optimum Tidal Volume from the Breathing Frequency, Body Weight and Sex of the Patient.*

pCO_2 of 40 mm. of mercury. The nomogram simply performs this calculation automatically.

The nomogram is designed to give the tidal volume necessary to meet basal conditions. Since many of the patients on whom it will be used will not be in the basal state, or may require an alveolar pCO_2 lower than 40 mm., certain corrections have been worked out to be added to the tidal volume as obtained from the nomogram.

Daytime Rise in Carbon Dioxide Production

Ten per cent should be added to the tidal volume during daytime to allow for metabolic needs after eating and minor muscular activity — this applies to patients in respirators.

Fever

Five per cent should be added for each degree of temperature above 99°F. (by rectum).

Altitude

Five per cent should be added to the tidal volume for each 2000 feet of altitude above sea level.

Metabolic Acidosis during Anesthesia

Twenty per cent should be added for patients under anesthesia with agents known to cause a metabolic acidosis. (This correction is approximate and is intended only to ensure that moderate hyperventilation is present; it should be considered optional at the discretion of the anesthesiologist.)

Changes in Respiratory Dead Space

When a tracheotomy or an endotracheal tube is in use, the dead space is decreased. An approximate correction may be made by subtraction of a volume equal to half the body weight in pounds. In anesthesia the dead-space volume of the apparatus and mask must be added if present.

These corrections are summarized in Figure 1. It should be noted that all corrections are individually calculated from the basal tidal volume and then added. The use of these corrections in poliomyelitis and in anesthesia is shown by the following sample calculations for a febrile patient with respiratory paralysis and a patient under ether anesthesia.

For a 120-pound female patient with respiratory paralysis, with the respiratory rate set at 18 per minute and a temperature of 104°F., awake, after a tracheotomy and after a meal, at an altitude of 3000 feet, the basal tidal volume is 290 cc. (see line drawn on Figure 1), with the following corrections:

Awake, post-prandial, +10%..	+10%	=	+29cc.
Fever, 5° x 5%	+25%	=	+73cc.
Altitude 1 ½ x 5%	+7½%	=	+22cc.
Tracheotomy $-\frac{120}{2}$		=	−60cc.
Required tidal volume predicted from nomogram and corrections			354cc.

Required minute ventilation =
354 x 18 = 6370 cc./min.

For a 180-pound, afebrile anesthetized (ether) male patient, with the respiratory rate at 12 per minute, at sea level and with an endotracheal tube in place (dead space of apparatus, 100 cc.), the basal tidal volume is 550 cc. (see line drawn on Figure 1), with the following corrections:

Fever 0			
Altitude 0			
Acidosis +20%		=	+110cc.
Endotracheal tube $-\frac{180}{2}$		=	− 90cc.
Apparatus dead space			+100cc.
Required tidal volume predicted from nomogram and corrections			670 cc.

Required minute ventilation =
670 x 12 = 8040 cc./min.

To test the accuracy of the nomogram in predicting proper ventilation, poliomyelitic patients with acute or chronic respiratory-muscle paralysis were studied while using chest respirators or breathing spontaneously. Their carbon dioxide production and respiratory dead space were measured and employed to calculate their "ideal" tidal volume at the observed frequency. After a period of three to five minutes to allow for washout of the collecting system, expired air samples were obtained for a period of two to four minutes. Arterial blood samples were drawn continuously over the same period. The samples were analyzed for carbon dioxide production, oxygen consumption and arterial pCO_2. Mean tidal volumes were obtained by division of the total expired volume by the number of breaths. The respiratory quotients (R_E or carbon dioxide produced divided by oxygen consumed) were also calculated; only patients whose R_E lay between 0.76 and 0.90 were assumed to be in a respiratory steady state and used for comparison with the nomogram. The respiratory dead space was calculated from the observed data by means of the Bohr equation. From the observed carbon dioxide production the effective or alveolar minute ventilation may be calculated at a given pCO_2.[17] The "ideal" tidal volume was therefore calculated as the tidal volume (measured at 24°C. saturated with water vapor) necessary to give a mean alveolar pCO_2 of 40 mm. of mercury at the observed breathing frequency. Table 1 gives a summary of these data on 1 patient with acute and 12 patients with chronic poliomyelitis and on 3 normal subjects. All the poliomyelitic patients were studied in the supine position, whereas the normal subjects were sitting. In Table 1 the ideal tidal volume has been compared with the tidal volume obtained from the nomogram (10 per cent has been added to the nomogram values because all measurements were made two or three hours after breakfast).

As shown by the percentage error in Table 1 there was good agreement between the tidal volume predicted from the nomogram and the "ideal" tidal volume. Some of the discrepancy may have been due to errors in the measured data — for example, the determination of the partial pressure of carbon dioxide in the arterial blood has an error of ±2 mm. of mercury; errors here influence the calculated dead space. Although the patients selected were considered to be in a steady state because their R_E values were between 0.76 and 0.90, this was an average value obtained during the interval of collection and gave no information regarding the variability of the R_E during that time. Wide variations in carbon dioxide production may be observed if shifts to or from the carbon dioxide stores in the body are occurring during the measuring period.

The data in Table 1 indicate that the nomogram is applicable to patients with poliomyelitis in spite of the fact that body-weight changes caused by muscle wasting or obesity might be expected to produce errors in predicted carbon dioxide production and dead space. In most of the subjects the tidal volume obtained from the nomogram differed from the ideal tidal volume owing to differences between the predicted and observed dead-space volumes. In 2 patients (F.E. and H.J.) the observed carbon dioxide production was much lower than that predicted from the body weight. Both these patients had considerable replacement of muscle mass by adipose tissue; the single determination of carbon dioxide production in H.J. may also have been in error for the technical reasons cited above.

The nomogram was also tested against the ideal tidal volumes for 10 normal male medical students, whose CO_2 production and respiratory dead space were calculated from expired and alveolar gas samples obtained during student experiments.[18] The nomogram value differed by +6±9.5 per cent for these subjects. Thus, for both groups in which the nomogram has been checked, the agreement is +5± 10 per cent. As corrected for the postprandial state, the nomogram gives slightly high values, which are preferable. The nomogram has also shown satisfac-

TABLE 1. *Data in Patients with Poliomyelitis and in Normal Subjects.*

Patient	Sex	Age	Body Weight	Duration of Disease	Respiratory Assistance	Carbon Dioxide Production	R_E	Arterial pCO_2	Respiratory Frequency	Mean Tidal Volume*	Respiratory Dead Space	Ideal Tidal Volume*†	Nomogram (+10%)	Error in Nomogram
		yr.	lb.			cc./min.		mm.Hg.	cyc./min.	cc.	cc.	cc.	cc.	%
Acute poliomyelitis:														
M.Hu.	F	8	57	4 days	No	128	0.81	31	42.5	131	53	113	121	+7.0
Chronic poliomyelitis:														
M.Ho.	F	14	82	9½ mo.	No	159	0.76	25	24.5	279	71	201	194	−3.0
W.S.	M	24	92	19 mo.	Yes	139	0.85	28	18.5	350	136	286	286	0
E.S.	F	25	96	29 mo.	No	154	0.81	36	17.6	276	82	257	281	+9.0
F.R.	M	27	90	40 mo.	Yes	152	0.85	32	14.9	365	108	312	325	+4.0
J.P.	M	27	115	10 mo.	Yes	200	0.80	32	14.5	489	144	420	385	−8.0
M.L.	M	27	161	8½ mo.	No	245	0.87	38	27.5	313	124	302	352	+17.0
M.C.	F	28	87	11 mo.	No	153	0.86	32	30.0	202	123	227	193	
				15½ mo.	No	138	0.76	48	11.2	323	119	365	363	
						146			20.6		121	(263)	(242)	−8.0
M.Hi.	F	29	87	10 mo.	Yes	174	0.87	25	18.0	356	47	240	264	+10.0
P.Y.	M	29	107	5 mo.	No	178	0.86	43	16.0	382	173	395	352	−11.0
S.L.	F	31	91	24 mo.	Yes	146	0.80	42	16.7	279	109	284	281	−1.0
F.E.	M	32	156	10 mo.	Yes	206	0.76	44	16.4	393	164	415	451	
				18 mo.	Yes	156	0.76	45	16.8	321	149	334	435	
				18½ mo.	Yes	180	0.84	44	16.6	341	144	361	440	
					Yes	184	0.80	44	16.7	334	134	354	435	
						182			16.6		148	(367)	(440)	+20.0
H.J.	M	37	154	16 mo.	Yes	177	0.81	37	16.7	359	126	338	435	+29.0
Normal subjects:														
I.B.	M	33	160	—	—	198	0.82	32	17.6	480	198	423	440	+4.0
B.F.	M	34	182	—	—	245	0.76	39	11.0	646	195	640	660	+3.0
B.K.	M	36	145	—	—	294	0.87	31	13.0	663	70	522	495	−5.0
			Mean & standard deviation of % error (all subjects)											+4±10.5%

*Measured at 24°C., ambient pressure, saturated with water vapor.
†Average tidal volume necessary to give alveolar CO_2 pressure of 40 mm. of mercury at observed frequency.

tory correlation with respiratory data obtained in 3 fasting newborn infants.[19] Because a considerable contribution to the scatter of these results was introduced by unavoidable errors in the measuring technics the standard deviation reflects in part the uncertainty of determining the true ideal tidal volume.

Methods and Sources of Error in Measuring Ventilation

If the nomogram is to be used as a guide, the actual ventilation in terms of mean tidal volume and breathing frequency must be measured for comparison. If the measured tidal volume corresponds to that obtained from the nomogram at the observed breathing frequency, proper therapy is being provided; otherwise, steps must be taken to alter the ventilation. The general principle of measuring ventilation is simple. A device such as a spirometer or gas meter is connected to the patient through a mouthpiece or mask or directly to a tracheotomy or endotracheal tube, and the respiratory excursions are recorded over a sufficient number of breaths. In practice, errors may be introduced either by the measuring device or inadvertently by the patient. Errors may also arise from the apparatus if leaks are present, if it adds to the respiratory dead space or if it imposes a resistance to the patient's breathing. The conscious patient may introduce errors, moreover, by altering his ventilation during the measuring period. The last source of error is very common.

During closed-circuit anesthesia the measurement of ventilation is comparatively easy. The patient can be observed continuously, there is no problem of cooperation, and leaks are easy to check. A metering device inserted in either the inspiratory or the expiratory line can record the total respired volume during an interval in which the number of breaths is counted. This permits calculation of the average tidal volume breathed spontaneously or delivered by the anesthesiologist. An example of the incorporation of a ventilation meter into anesthesia apparatus has been reported by Stead et al.[11] and Zinberg and Jensen.[20] Another solution lies in the use of anesthesia devices such as those described by Anderson, Crafoord and Frenckner[21] and Musgrove,[22] which can be set to deliver the required ventilation automatically. Since the equipment for ventilation measurements during anesthesia requires special adaptation to existing apparatus, it is not discussed further in this report.

One of the simplest devices for recording ventilation in conscious subjects is a spirometer. The best technic is to measure the expired or inspired volume only, by means of a low-resistance-valve arrangement connected to a mouthpiece such as that in Figure 2.* Since most commercially available spirometers have a capacity of about 6 liters, at least thirty or forty seconds' observation is usually possible. This period should be ample for determining the breathing frequency and mean tidal volume. A standard machine for calculation of basal metabolic rates may also be adapted for ventilation measurements. For best results it should be used with the soda-lime container (carbon dioxide absorber), and the internal valves removed. The purpose of these modifications is to keep the resistance of the system as low as possible. When external valves such as those shown in Figure 2 are included, a standard apparatus for determining basal metabolism is an adequate recorder. Without valves — that is, with the subject rebreathing into the spirometer — only four or five breaths will be possible before carbon dioxide will accumulate to the point where the ventilation will be changed. After the rebreathing period the spirometer should be flushed out between measurements to remove carbon dioxide. Provided that these reservations are kept in mind a spirometer for determination of basal metabolic rate can be used without any added equipment, but five or six successive measurements will be necessary to get a good average of the tidal volume. Ventilation can also be determined by collection of the expired air in a bag (such as a Douglas bag) and measurement of the expired volume in a spirometer. For example, the bag technic used to determine maximum breathing capacity will indicate resting ventilation as well.

Figure 2. *Spirometer and Low-Resistance Valve for Measuring Resting Ventilation.*

*Obtainable from Warren E. Collins Company, Boston.

Recently, so-called dry-gas meters, which operate in the same way as household gas meters, have become commercially available for measuring ventilation. Two examples are shown in Figure 3. These meters have a low resistance and are very convenient for repeated measurements. They can be used with a mouthpiece and nose-clip, mask or tracheotomy-tube adapter, to measure the volume of inspired air. The Bennett ventilation meter* is small and easily portable although it has the disadvantage of being very fragile and has a larger dead space than the Emerson.† Both these types become inaccurate at high flow rates, but at resting flow rates they are satisfactory.

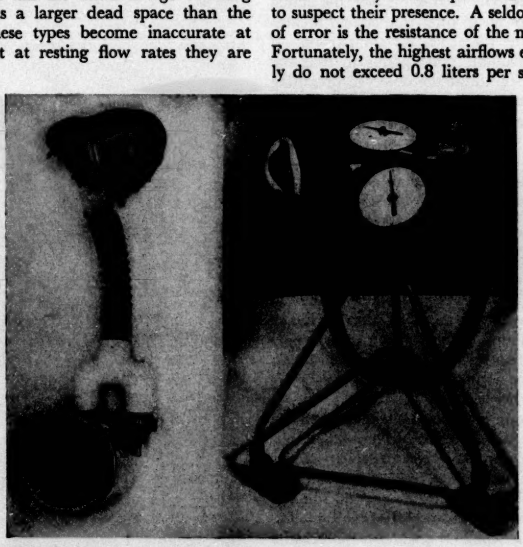

FIGURE 3. *Ventilation Meters.*
On the left is the Bennett hand model, and on the right the Emerson Breathometer.

When the ventilation of a patient is measured while he is being given artificial respiration in tank or cuirass respirators, errors may arise because of involuntary changes imposed by the patient. Even when he has complete respiratory paralysis, he may resist ventilation during the measuring period by partial closure of his glottis. If he has some residual respiratory strength he may assist or oppose the respirator and change his ventilation during the procedure. These changes make the measured ventilation atypical of the patient's true ventilation while he is unobserved, and the respirator settings may be altered because the values do not correspond to the nomogram. *Changes in ventilation that may occur when any conscious subject knows that his respiration is being measured probably represent the most important source of error in ventilation measurements.* The only way in which this type of error can be overcome is to repeat the procedure often enough (usually four or five times) for the subject to be able to relax and breathe naturally in the respirator during the measuring period. That the "relaxed" ventilation has been obtained may be indicated by the constancy of successive ventilation measurements.

Leaks in the instrument or in the mouthpiece or mask assembly may lead to errors. Elimination of leaks is usually obvious provided the physician is alert to suspect their presence. A seldom recognized source of error is the resistance of the measuring apparatus. Fortunately, the highest airflows encountered generally do not exceed 0.8 liters per second, and the majority will be under 0.5 liters per second. If the resistance of the apparatus is high, these flow rates will give low tidal-volume readings because of the added mechanical load. In this case the tank or cuirass pressures may be increased, and when the device is removed from the patient, the stage will be set for hyperventilation. This is another example of how the measured ventilation may not be typical of the resting unobserved ventilation. The gas meters shown in Figure 3 are designed to have a low resistance and avoid this source of error. If the diameter of the tubing and connectors is kept large and high-resistance valves[23] (such as the Sadd valves present in the usual machine for calculation of basal metabolic rates) are eliminated, a spirometer can be made to have a sufficiently low resistance for these purposes.

Special precautions may be necessary to measure ventilation in certain cases. For example, children will require a longer time to get used to the apparatus

*Available from J. J. Monaghan Company, Denver, Colorado.
†Available from J. H. Emerson Company, Cambridge, Massachusetts.

and should be allowed several trials until they are familiar with the procedure. With young children and infants a nose-clip cannot be used. Although in such cases a mask is a satisfactory substitute for the mouthpiece, the proportionately large added dead space of the mask will lead to changes in ventilation if more than a few breaths are measured at a time. In determination of the ventilation through a tracheotomy, it is most important that the adapter to the equipment does not encroach on the tracheotomy tube. Tracheotomy tubes with extensions of the inner tube above the plate, which allow adapters to be fitted on the outside of the inner tube, have been found suitable for ventilation measurements at the Mary MacArthur Respirator Unit. If such a modified type of tracheotomy tube is not available, a section of plastic tubing, 3 or 4 cm. in length, with a diameter the same as that of the inner tube, can be fitted into the outer tube and connected to the spirometer or ventilation meter. It is necessary to close the nose and mouth when the ventilation is measured through a tracheotomy tube, and leaks around the tracheotomy tube must be avoided.

Discussion

To use the nomogram intelligently, the physician must be clearly aware of its limitations. The derivation of the nomogram depends on three major assumptions: the basal carbon dioxide production may be predicted from the body weight; the respiratory dead space may also be predicted from the body weight, and the optimum arterial pCO_2 is 40 mm. of mercury. The corrections to the nomogram are designed to permit certain exceptions to these fundamental assumptions. Thus, the activity and fever corrections take into account a rise above the basal carbon dioxide production, and the altitude and acidosis corrections provide for modification of the pCO_2. In conditions in which metabolism is altered from basal levels, such as thyroid disease or muscular activity, the nomogram should not be relied upon. Although the treatment of other metabolic acid-base changes is generally directed toward the underlying cause, (dehydration, diabetic acidosis and so forth) in some cases, such as chronic nephritis, respiratory adjustment of pH may be necessary, and the optimum pCO_2 is no longer 40 mm. Finally, some patients may have an increase in respiratory dead space owing to lung disease, as with severe emphysema. In all these cases the assumptions behind the nomogram do not hold, and the physician should not apply it when giving artificial respiration.

These exceptional circumstances underscore the fact that the nomogram should be considered simply as a guide to proper ventilatory levels. In view of the possible sources of error in ventilation measurements, as well as exceptions to the basic assumptions of the nomogram, it is clear that the physician responsible for providing prolonged artificial respiration must continue to exercise sound clinical judgment in assessing the effectiveness of ventilatory therapy.

Summary and Conclusions

For artificial respiration to be adjusted to a patient's needs, particularly when it is given for prolonged periods, the physician must closely regulate the amount of ventilation provided. A nomogram is described that gives the proper tidal volume to be supplied to a patient at any given breathing frequency. Adequacy of artificial respiration may be determined by measurement of the mean tidal volume and comparison of the measured value with that obtained from the nomogram.

The nomogram is designed to provide for carbon dioxide removal. Under some pathologic conditions, such as heart or lung disease, hypoxia may be present in spite of adequate ventilation. The treatment of hypoxia is by oxygen therapy or, if possible, by correction of the underlying disease, rather than by increase in ventilation.

Some of the simpler methods of ascertaining ventilation are discussed. These include use of a spirometer or a low-resistance gas meter. Errors in ventilation measurements may arise because of leaks, high resistance or added respiratory dead space in the measuring system, and poor relaxation by the subject.

The nomogram is intended as a guide to be applied to patients with normal metabolism, acid-base regulation and respiratory dead-space volume. The physician using it must exercise clinical judgment in determining when these normal conditions no longer apply.

We are indebted to Dr. James L. Whittenberger for his encouragement and advice, to Miss Libby Servello for performing the analyses of blood and expired air and to Dr. C. D. Cook for the use of his data obtained on newborn infants.

References

1. Whittenberger, J. L., and Sarnoff, S. J. Symposium on specific methods of treatment: physiologic principles in treatment of respiratory failure. *M. Clin. North America* **34**:1335-1362, 1950.
2. Astrup, P., Getsche, H., and Neukirch, F. Laboratory investigations during treatment of patients with poliomyelitis and respiratory paralysis. *Brit. M. J.* **1**:780-786, 1954.
3. Grulee, C. G., Jr. Diagnosis of acute poliomyelitis. *Postgrad. Med.* **14**:347-350, 1953.
4. Brown, E. B., Jr., Campbell, G. S., Johnson, M. N., Hemingway, A., and Visscher, M. B. Changes in response to inhalation of CO_2 before and after 24 hours of hyperventilation in man. *J. Appl. Physiol.* **1**:333-338, 1948.
5. Collier, C. R., and Affeldt, J. E. Ventilatory efficiency of cuiras respirator in totally paralyzed chronic poliomyelitis patients. *J. Appl. Physiol.* **6**:531-538, 1954.
6. Stormont, R. T., Hathaway, H. R., Shideman, F. E., and Seevers, M. H. Acid-base balance during cyclopropane anesthesia. *Anesthesiology* **3**:369-378, 1942.
7. Beecher, H. K., and Murphy, A. J. Acidosis during thoracic surgery. *J. Thoracic Surg.* **19**:30-70, 1950.
8. Taylor, F. H., and Root, A. Disturbances in acid-base balance during ether anesthesia, with special reference to changes occurring during thoracic surgery. *J. Thoracic Surg.* **20**:289-295, 1950.
9. Gibbon, J. H., Jr., Albritten, F. F., Jr., Stayman, J. W., Jr., and Judd, J. M. Clinical study of respiratory exchange during prolonged operations with open thorax. *Ann. Surg.* **132**:611-625, 1950.
10. Etsten, B. E. Respiratory acidosis during intrathoracic surgery: (Overholt) prone position. *J. Thoracic Surg.* **25**:286-299, 1953.
11. Stead, W. W., Martin, F. E., and Jensen, N. K. Physiologic studies following thoracic surgery, IV. Mechanism of development of acidosis during anesthesia. *J. Thoracic Surg.* **25**:435-447, 1953.
12. Van Slyke, D. D., Austin, J. H., and Cullen, G. E. Effect of ether anesthesia on acid-base balance of blood. *J. Biol. Chem.* **53**: 277-292, 1922.
13. Cullen, G. E., Austin, J. H., Kornblum, K., and Robinson, H. W. Initial acidosis in anesthesia. *J. Biol. Chem.* **54**:625-661, 1923.

14. Bunker, J. P., Brewster, W. P., Smith, R. M., and Beecher, H. K. Metabolic effects of anesthesia in man. III. Acid-base balance in infants and children during anesthesia. *J. Appl. Physiol.* 5:233-241, 1952.
15. Benedict, F. G., and Talbot, F. B. *Metabolism and Growth from Birth to Puberty.* (Publication No. 302.) Washington, D. C.: Carnegie Institution, 1921.
16. Harris, J. A., and Benedict, F. G. *A Biometric Study of Basal Metabolism in Man.* (Publication No. 279.) Washington, D. C.: Carnegie Institution, 1919.
17. Fenn, W. O., Rahn, H., and Otis, A. B. Theoretical study of composition of alveolar air at altitude. *Am. J. Physiol.* 146:637-653, 1946.
18. Mead, J. Personal communication.
19. Cook, C. D., Kariberg, P., Cherry, R. B., O'Brien, B., and Smith, C. A. Unpublished data.
20. Zinberg, S., and Jensen, N. K. Method for measuring tidal and minute volumes in patients under regional and general anesthesia. *J. Thoracic Surg.* 28:85-89, 1954.
21. Anderson, E., Crafoord, C., and Frenckner, P. New and practical method of producing rhythmic ventilation during positive pressure anaesthesia. *Acta otolaryng.* 28:95-102, 1940.
22. Musgrove, A. H. Controlled respiration in thoracic surgery: new mechanical respirator. *Anaesthesia* 7:77-83, 1952.
23. *Methods in Medical Research.* Vol. 2. Edited by J. H. Comroe, Jr. 361 pp. Chicago: Year Book Publishers, 1950. Pp. 79 and 80.

HISTOPLASMOSIS*

Report of a Case, with Observations on Management

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THE acquisition of knowledge concerning the clinical features of histoplasmosis has followed that of many other newly recognized diseases. In 1906 Darling[1] described a rapidly fatal disease involving primarily the reticuloendothelial system. Except for occasional reports, the next step was the recognition, in 1940,[2] that asymptomatic pulmonary calcifications could result from infection by *Histoplasma capsulatum*. Since that time the gaps between the two extremes are being filled in. Outbreaks of mild atypical pneumonia, ulcers of the mucous membranes, pulmonary cavitation, chronic disseminated pulmonary disease and a variety of other lesions have been recognized. The purpose of this report is threefold: to re-emphasize an infrequently recognized syndrome caused by *H. capsulatum* — namely, a diffuse pulmonary infiltrative variety with ensuing capillary-alveolar block; to comment on the effect of cortisone on clinical and serologic response; and to indicate possible therapeutic effects of β-diethylaminoethyl fencholate.§

CASE REPORT

A 28-year-old feed-store employee was admitted to the hospital on November 2, 1953, in acute respiratory distress with fever and cough. Three years previously he had been hospitalized elsewhere with an illness characterized by fever and malaise. Biopsies were done of the bone marrow and the liver, and he was told that he had an enlarged liver and spleen, probably caused by infectious hepatitis. After this, he was asymptomatic until 6 months before admission, when he noticed transient substernal and precordial pains and mild dyspnea on exertion. The chest pain disappeared within 3 months. About 2 months before admission evening fatigue, accompanied by a temperature of from 99-100°F., developed. One month later dyspnea increased and became more troublesome. On October 5 he consulted a physician, who found scattered musical rales in both lung fields. A chest film showed marked peribronchial infiltration of a soft, fluffy character. He was given a total of 8 gm. of oxytetracycline, and a bronchoscope was passed, with aspiration of yellowish secretions. Fungi were not found on culture. By October 20 he had begun to cough continuously, with maximum temperature of 104°F. Three days before admission a severe sore throat developed, and he had repeated shaking chills.

Physical examination disclosed a well developed and well nourished, acutely ill and cyanotic man who coughed frequently. The throat was reddened, and there were several 5 mm. yellowish-white plaques covering both hard and soft palate; these areas did not bleed when scraped. Diffuse, fine, crackling rales were heard over both lower lobes posteriorly and over the right middle lobe and the lingula on the left. The liver edge was palpated 4 fingerbreadths below the right costal margin, and the spleen 2 fingerbreadths below the left costal margin. Both were firm and nontender.

The temperature was 102.4°F. (by rectum), the pulse 108, and the respirations 32. The blood pressure was 100/70.

Examination of the blood revealed a hemoglobin of 17 gm. per 100 cc. and a white-cell count of 10,250, with 57 per cent neutrophils, 13 per cent band forms, 21 per cent lymphocytes, 7 per cent monocytes, 1 per cent eosinophils and 1 per cent myelocytes. The sedimentation rate was 58 mm. per hour. During November the white count slowly fell to a low of 1250, and the hemoglobin to 9.3 gm. per 100 cc. On December 31, soon after treatment with β-diethylaminoethyl fencholate was started and general improvement was noted, the hemoglobin had risen to 13.2 per 100 cc., and the white-cell count to 6000. No essential change was noted in the differential count during this time. Skin tests with histoplasmin and 1st-strength PPD were negative on admission.

The urine on admission contained a trace of albumin, with rare red cells and hyaline and granular casts, which cleared within 4 days. On November 3 a bromsulfalein test showed 36 per cent retention in ½ hour. On the following day the bilirubin was 0.1 mg. per 100 cc., thymol turbidity 1.9 units, and cephalin flocculation +++; the total protein was 5.8 gm. per 100 cc., with an albumin of 3.0 and a globulin of 2.8 gm. per 100 cc. On November 10 the bromsulfalein retention was 9 per cent in 30 minutes. Five days later the bilirubin was 2.1 mg. per 100 cc. (1.6 mg. direct and 0.5 mg. total); the bromsulfalein retention was 34 per cent. On December 22 the bilirubin was 2.7 mg. per 100 cc. (1.0 mg. direct and 1.7 mg. total), and a 2-hour urinary urobilinogen was 1.3 Ehrlich units. By December 30 the bilirubin was 1.4 mg. per 100 cc. (0.6 mg. direct and 0.8 mg. total); the total protein was now 6.7 gm. per 100 cc., with 2.4 gm. of albumin and 4.3 gm. of globulin. On January 13 thymol turbidity was 18 units, and cephalin flocculation +++ in 48 hours.

An x-ray film of the chest (Fig. 1) on admission demonstrated a diffuse area of increased density throughout both lung fields that was more striking at the hilar regions and at the base. The densities coalesced, and there was no hilar enlargement. Films on November 4 and November 6 showed no change. On November 9 there was considerable clearing in the periphery. Three days later no change was apparent. By November 17 there was further moderate clearing of the fine peribronchial and perivascular infiltration

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§Kindly supplied as MRD-112 by Dr. Gerald Morson, of the William S. Merrell Company, Cincinnati, Ohio.

in the peripheral thirds of both lungs, with a residuum in both parahilar and right-cardiophrenic-angle areas. On November 23 the slight clearing had continued, and the increased perihilar markings were regressing; no conglomerate areas remained. No further change was noted until December 8, when slight progression of the lesions, particularly on the right, was noted. A week later the infiltrates in the right lower lung and the left mid-lung field had increased. By December 21 clearing was again evident, persisting in the film taken on December 30 (Fig. 2). There was no change in a film taken on January 21. On March 17 no further changes or calcifications were observed.

The frequent isolation of *H. capsulatum* from clinical materials during the period in the hospital leaves no doubt of the etiology of the present illness. A throat culture taken at the time of admission was negative for fungi (Fig. 3); however, it was discarded after 1 week. Soon after cortisone was given a heavy growth of *Candida albicans* appeared, persisting until the hormone was discontinued. A helpful cultural technic used was the substitution of a Castaneda type of blood-culture setup[3] containing Sabouraud's agar, instead of the usual liquid-blood-culture flask. Citrated blood was poured over the surface of the agar, and the bottle was agitated daily. Colonies appeared on the agar in 12 days and were identified by microscopical examination. (Under the usual blood-culture method, colonies

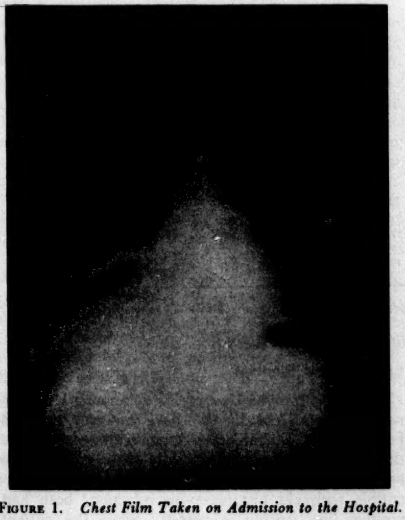


FIGURE 1. *Chest Film Taken on Admission to the Hospital.*

fished from broth cultures have to be subcultured to Sabouraud's agar for final identification, since typical morphology is seen only on this agar.)

On the day of admission (Fig. 3) the temperature rose to 105°F.; acute respiratory distress developed and oxygen was required. Antibiotics (oxytetracycline and penicillin) were begun on the 2d day. With digitalization and supportive measures the patient appeared to improve. The sore throat improved, but the rales persisted. In the belief that the illness represented sarcoidosis, cortisone administration was begun on November 4. The temperature had begun to fall, however, before this agent was given. He continued to improve, and, by November 9, the chest film had shown clearing for the first time. By November 24 fever had begun to recur despite continued cortisone dosage of 300 mg. a day. At this time, the histoplasma complement-fixation titer was reported as 1:1040.* Consequently, it was deemed advisable to discontinue cortisone therapy. The dosage was decreased gradually, and the drug discontinued on December 5. The film of December 8 for the first time showed a worsening of the chest lesions, with further progression by December 15. By December 20, however, on no medication, clearing had again begun to occur. From November 25 to December 25 the same signs seen on admission developed. The spleen and liver were again palpable; the sore throat returned, this time without the growth of candida but with histoplasma being cultured. Several transfusions and other supportive therapy were given during this time. Ascites, signs of hypersplenism with hemolysis and leukopenia developed, and the patient appeared moribund. On Decem-

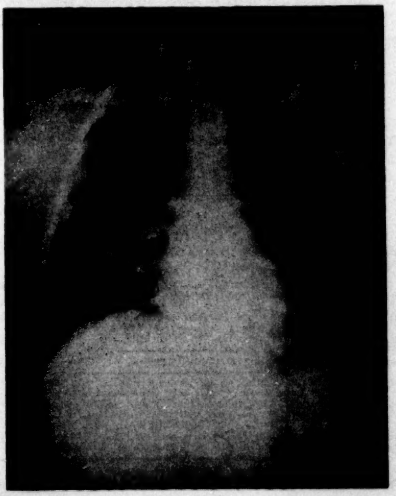


FIGURE 2. *Chest Film Taken on December 30, Showing Maximum Improvement.*

ber 17 histoplasma complement-fixation tests showed a rise in titer to 1:32,768. On December 26, 5 days after he appeared to have a remission of this relapse, β-diethylaminoethyl fencholate was started in a dosage of 50 mg. intravenously each day. By December 29 the temperature was down to 100°F.; the spleen was no longer palpable, and he appeared better clinically. The histoplasmin skin test was positive for the first time on December 21. On January 5 the daily dose was increased to 150 mg., intravenously, and this was followed by onset of drowsiness, which failed to respond to dextro-amphetamine sulfate. By January 10 the patient had begun to appear alert and was eating well, although he still complained of a sore throat. The last dose of β-diethylaminoethyl fencholate was given on January 20. Two days later the fever had subsided, and he appeared quite well. Just before discharge, a chest film revealed little change in the pulmonary infiltration from that seen on a previous film taken when the infiltration had cleared peripherally on cortisone therapy. Two months later, at follow-up examination, he was gaining weight and was asymptomatic. A chest film at that time showed no remarkable change in the pulmonary infiltration and there were no calcifications; the complement-fixation titer was down to 1:4,020.

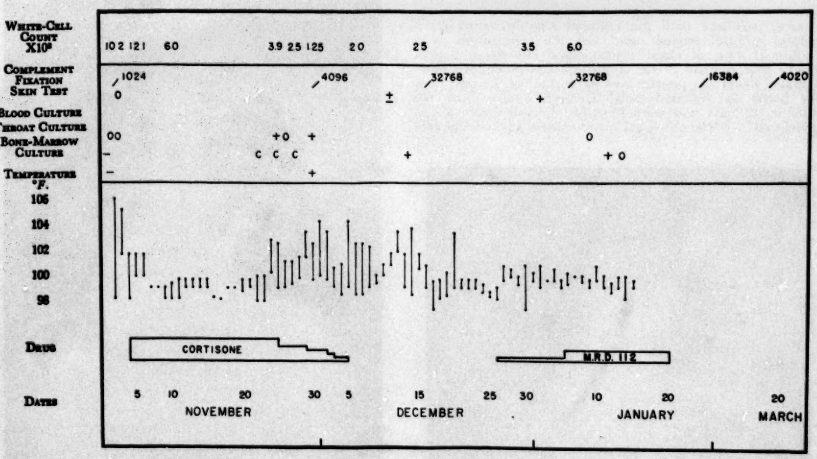
*These tests were conducted by the Communicable Disease Center, Serology Laboratory, United States Public Health Service, Chamblee, Georgia.

Discussion

Mycologic and Serologic Findings

The organism isolated from the bone marrow, blood stream and throat of this patient appeared to be a typical strain of *H. capsulatum*. It was considered that this strain might be one of animal origin described by Emmons, Morlan and Hill,[4] in their work on rats and skunks in Georgia; Dr. Emmons kindly examined a slide preparation of the fungus, which he considered typical of human strains. On the third hospital day, a lesion appeared just below the left eye. It was scaly, with a slightly moist border. Scrapings from this, stained by Wright's method, revealed the presence of numerous budding, yeast-like cells approximately 10 microns and other forms, 3 or 4 microns, resembling histoplasma. All efforts to culture *H. capsulatum* from this lesion failed, supporting the impression that the budding, somewhat bottle-shaped yeast cells were *Pityrosporum ovale*.

The serologic picture that developed is unusual in view of what has previously been considered an average immunologic response in this disease. Titers of 1:160 to 1:360 have generally been considered high, but, in the present case, a titer of 1:32,768 was obtained on more than one occasion. Campbell[8] recently pointed out that the demonstration of complement-fixing antibodies in cases of histoplasmosis may well depend on whether an optimal dilution of the yeast-phase antigen or the broth-filtrate antigen, histoplasmin, is used. A significant titer to the former denotes early disease, whereas chronic disease is identified by significant titer with the latter. In the case reported above, the broth-filtrate antigen was used, suggesting that the patient had chronic disease. The negative skin test on admission probably resulted from anergy caused by the overwhelming infection. It is difficult to account for the exceptionally high titer that developed while he was under observation except to consider the infecting strain of histoplasma a potent immunizer or to believe that cortisone altered the antibody response. Neither of these hypotheses has so far been substantiated in experiments in which guinea pigs were infected with the patient's strain.


White-Cell Count X10³
10.2 12.1 6.0 3.9 2.5 1.25 2.0 2.5 3.5 6.0
Complement Fixation Skin Test
1:4 1:8 1:16 1:32 1:64 1:128 1:256 1:512 1:1024 1:2048 1:4096 1:8192 1:16384 1:32768 1:65536
0 ± + 0 ± + + +

the diagnosis of histoplasmosis became apparent, the drug was discontinued because of its recognized deleterious effects on a variety of infectious processes[8]; the suggestion has been made that cortisone is contraindicated in the management of histoplasmosis.[9] Indeed, a case of a fulminating form of histoplasmosis in a patient receiving cortisone for exfoliative dermatitis has been described.[10] Israel et al.[11] gave 200 mg. of cortisone daily for ten days to a patient with chronic disseminated histoplasmosis with many features of sarcoidosis. The drug, which was given because of some evidence of adrenal insufficiency, had no discernible effect. Farrell and his associates[12] studied the action of cortisone on experimental histoplasmosis in dogs. Whereas the intratracheal instillation of mycelia of *H. capsulatum* into control animals resulted in a positive skin test and no evidence of disease, the same procedure in cortisone-treated dogs produced a rapidly fatal disseminated form of the disease. Salvin and Furcolow[13] described a patient with all the clinical features of sarcoidosis from whom no histoplasma was isolated or seen in muscle and lymph-node biopsy but was isolated from gastric washings. The histoplasmin skin test did become positive under observation. After four weeks of cortisone therapy the ocular lesions improved, and lymph nodes decreased in size, with slight clearing of lungs on x-ray study. It is our opinion, however, that their case may have represented sarcoidosis rather than histoplasmosis.

We have the impression that, in the case reported above, cortisone contributed greatly to the clearing of the acute pulmonary lesions. In granulomatous processes similar to histoplasmosis cortisone has been shown to cause disappearance of lesions, particularly the acute ones. When the inflammation appears to serve a useful function, as in tuberculosis, its disruption by steroid therapy permits a dissemination of tubercle bacilli throughout the body. On the other hand, in conditions such as sarcoidosis and beryllium granulomatosis, this lysis of granulomatous tissue is often beneficial. Whether cortisone produced a dissemination of the organisms while clearing the inflammatory lesion cannot be stated. Although the temperature again rose before the cortisone dosage was lowered, the exacerbation of pulmonary lesions occurred after the drug was discontinued. Preliminary studies, which will be reported in detail later, indicate that in laboratory animals cortisone does enhance infection with *H. capsulatum*.[14]

β-diethylaminoethyl fencholate has been shown to be effective against a variety of fungi in vitro.[15] *H. capsulatum* is inhibited in a concentration of 0.1 mg. per cubic centimeter of agar. Whether it served a useful purpose in the case reported above is difficult to assess since the lesions had begun to show clearing before it was given. It is not easy to ascertain whether prompter clearing of lesions would have been obtained with larger doses. Except for slight drowsiness no toxicity was noted.

Summary

A case of acute histoplasmosis with features of the so-called capillary-alveolar-block syndrome is presented. Observations on the use of cortisone and β-diethylaminoethyl fencholate in this disease are recorded.

References

1. Darling, S. T. Protozoön general infection: Histoplasma capsulata producing pseudotubercles in lungs and focal necroses in liver, spleen and lymph nodes. *J.A.M.A.* **66**:1283-1285, 1906.
2. Mekney, H. E. Histoplasmosis (reticulo-endothelial cytomycosis); review with mention of 13 unpublished cases. *Am. J. Trop. Med.* **29**:605-616, 1940.
3. Castaneda, M. R. Practical method for routine blood cultures in brucellosis. *Proc. Soc. Exper. Biol. & Med.* **64**:114, 1947.
4. Emmons, C. W., Morlan, H. B., and Hill, E. L. Histoplasmosis in rats and skunks in Georgia. *Pub. Health Rep.* **64**:1423-1430, 1949.
5. Campbell, C. C. Antigenic fractions of *Histoplasma capsulatum*. *Am. J. Pub. Health* **43**:712-717, 1953.
6. Peeples, W. J., and Spence, M. J. Pulmonary cavitation due to *Histoplasma capsulatum*. *Am. Rev. Tuberc.* **69**:111-115, 1954.
7. Zeidberg, L. D., Ajello, L., Dillon, A., and Runyon, L. C. Isolation of *Histoplasma capsulatum* from soil. *Am. J. Pub. Health* **42**: 930-935, 1952.
8. Michael, M., Jr. Cortisone and ACTH in infectious processes. *In Monographs in Medicine*. Series 1. Edited by W. B. Bean et al. 655 pp. Baltimore: Williams and Wilkins, 1952. Pp. 271-294.
9. Shull, H. J. Human histoplasmosis: disease with protean manifestations often with digestive system involvement. *Gastroenterology* **25**: 582-595, 1953.
10. Fox, H. Exfoliative dermatitis complicated by fatal acute disseminated histoplasmosis. *Arch. Dermat. & Syph.* **68**:734-737, 1953.
11. Israel, H. L., DeLamater, E., Sones, M., Willis, W. D., and Mirmelstein, A. Chronic disseminated histoplasmosis: investigation of its relationship to sarcoidosis. *Am. J. Med.* **12**:252-260, 1952.
12. Farrell, R. L., Cole, C. R., Prior, J. A., and Saslaw, S. Experimental histoplasmosis. I. Methods for production of histoplasmosis in dogs. *Proc. Soc. Exper. Biol. & Med.* **84**:51-54, 1953.
13. Salvin, S. B., and Furcolow, M. L. Precipitins in human histoplasmosis. *J. Lab. & Clin. Med.* **43**:259-274, 1954.
14. Vogel, R., and Timpe, A. Unpublished data.
15. Ludwig, E. A., Murray, F. J., Smith, J. K., Thompson, C. R., and Werner, H. W. Laboratory studies on β-diethylaminoethyl fencholate, new antifungal agent. *Antibiotics & Chemother.* **4**: 56-61, 1954.

EMERGENCY THORACOTOMY FOR MASSIVE SPONTANEOUS HEMOPNEUMOTHORAX*

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MASSIVE intrapleural hemorrhage is a rare but frequently fatal complication of spontaneous pneumothorax for which surgical treatment has only recently been utilized. This article summarizes published data demonstrating that intrapleural hemorrhage in this condition frequently presents an indication for emergency thoracotomy. Preoperative management and the indications for and conduct of operation are briefly considered, and a typical case is briefly reported in which the hemorrhage did not assume serious proportions until four days after onset of the illness, when a positive pressure pneumothorax presumably developed and produced rupture of a vascular adhesion. By actual weight and measurement the intrapleural blood loss was 3975 cc.¶; 4000 cc. of blood and 500 cc. of plasma were administered before and during operation.

CASE REPORT

A 33-year-old truck driver was admitted to the hospital on October 27, 1953, because of sudden severe chest pain and dyspnea of 3 days' duration.

Physical examination showed a dyspneic and orthopneic man with signs of pneumothorax on the right. A roentgenogram of the chest (Fig. 1) demonstrated almost complete collapse of the right lung by pneumothorax; a moderate amount of "fluid" was present. On the following day the patient's condition was worse. The blood pressure was 100/70, and the pulse rate was 124; 500 cc. of plasma was administered. After this a closed thoracotomy with subaqueous deflation was done by a surgical resident. During the performance of this procedure approximately 500 cc. of blood was expelled through the trocar, and when the catheter was connected to the deflation system, a disconcertingly large amount of blood drained into the bottle. The blood pressure continued at hypotensive levels, and 1000 cc. of blood was administered. At 3 o'clock on the following morning, when the patient was first seen by one of us, 1500 cc. of blood had collected in the drainage bottle. At this time he was in severe shock, his skin was cold and moist, and he was alarmingly pallid. He improved during the administration of another 500 cc. of blood, but the blood pressure fell to shock levels again immediately after this transfusion had been completed. A roentgenogram of the chest was taken at the bedside at 8 a.m. (Fig. 2). Another 500 cc. of blood was then administered, and operation was done shortly thereafter. Before the thoracotomy 2500 cc. of blood and 500 cc. of plasma were administered. During the same period 2600 cc. of blood had collected in the drainage bottle.

At operation the lung was found to be completely collapsed, and the pleural space contained an additional 1375 cc. of liquid and clotted blood. The source of the hemorrhage was a severed apical parietal adhesion about 2 mm. in diameter. A cluster of emphysematous blebs in the apex of the upper lobe was excised. The patient's condition, which was precarious at the beginning of operation, improved immediately after evacuation of the blood and re-expansion of the lung.

The blood loss during the operation was 600 cc., and an additional 1500 cc. of blood was given during the procedure. At the end of the operation his condition was excellent. Recovery was without incident. He was ambulatory on the 2d day and was discharged from the hospital on the 9th day after operation. A roentgenogram of the chest taken on the 6th postoperative day is reproduced in Figure 3.

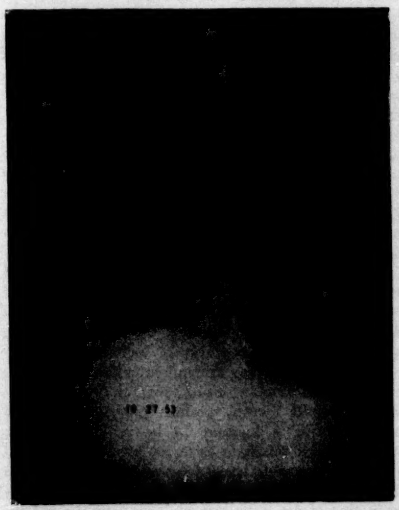

FIGURE 1. *Roentgenogram of the Chest Taken Three Days after the Onset of the Illness.*

The amount of fluid present is considerably larger than that seen in uncomplicated spontaneous pneumothorax. In this circumstance hemorrhage should always be suspected if more than a small amount of fluid is present.

GENERAL CONSIDERATIONS

Spontaneous hemopneumothorax is a form of the more familiar spontaneous pneumothorax as seen in apparently healthy persons.[1-3] The number of cases reported approximates 100,[2,4] with a mortality of about 20 to 25 per cent.[1,5,6] The disease is almost always nontuberculous and is due to rupture of an emphysematous bleb.[1,7-9] The first autopsy reports are those of Pitt[10] and Rolleston.[11] The latter's patient presented signs suggesting a perforated peptic ulcer; this feature has frequently been reported since

*Presented at a meeting of the Upstate Thoracic Society, Saranac Lake, New York, July 24, 1954.

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¶Not including approximately 500 cc. expelled through the trocar during the performance of the closed thoracotomy.

then, and in a few cases* exploratory laparotomies have been done.[2,3,12] The disease typically occurs in young male patients with an asthenic bodily habitus, and is usually ushered in by sudden pain, dyspnea and dry cough. Hemorrhage may occur at the onset, but apparently is often delayed for twenty-four to forty-eight hours.[1-3,13,14] When delayed hemorrhage occurs it is usually due to tearing of a vascular adhesion; hemorrhage from the lung at the site of the ruptured bleb is said to occur,[1,2,15] but appears to be less important since, in this circumstance, collapse of the lung has a distinct hemostatic effect. The source of the bleeding may be obscure at autopsy[9,12,15]; with 1 exception the source of the hemorrhage among the operative cases was the stump of a torn apical parietal adhesion.

Pathological Physiology

The clinical picture varies greatly, as might be expected, since in addition to hemorrhagic shock there may be various degrees of cardiorespiratory embarrassment from collapse of the lung, positive intrapleural pressures and mediastinal displacement. From a physiologic point of view the patient may present anoxia of anemic, stagnant and anoxic origin,[16] and for these reasons it is not surprising that several deaths within less than twenty-four hours have been reported.[12,15,17] When one considers that these deaths have frequently occurred in apparently healthy robust young males it is seen that hemopneumothorax has few parallels among diseases that may be rapidly fatal in patients in this age group.

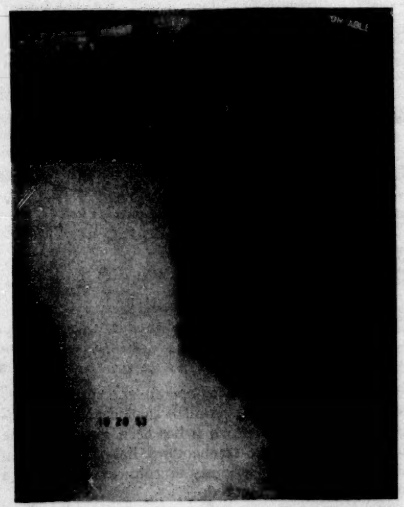

FIGURE 2. *Roentgenogram Taken Immediately before Operation.*

The catheter is seen in the second anterior interspace. The right hemithorax is almost completely filled with blood; at this time 2600 cc. of blood had accumulated in the drainage bottle.

*Such a patient observed by one of us was operated on a few hours after admission to the hospital. When first seen on the tenth day of his illness 1500 cc. of clotted blood was aspirated through a catheter. A persistent pneumothorax required thoracotomy and excision of leaking emphysematous blebs.

Preoperative Management

A strong case is currently being made for treating all patients presenting idiopathic spontaneous pneumothorax by closed thoracotomy and subaqueous deflation.[18] In addition to other advantages, this treatment should prevent the development of tension pneumothorax and tearing of vascular adhesions, with consequent intrapleural hemorrhage. Similar management, perhaps preceded by thorough catheter aspiration of the hemothorax,[19] appears to be a satisfactory initial therapeutic measure if the patient is seen early. Closed thoracotomy and subaqueous deflation should diminish the cardiorespiratory component and in substance tend to reduce the surgical problem to one of hemorrhage and shock.

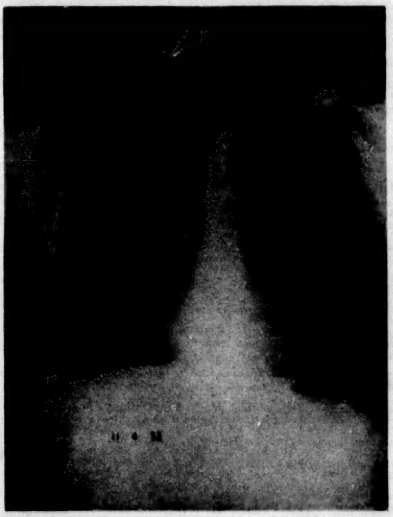

FIGURE 3. *Roentgenogram Taken on the Sixth Postoperative Day.*

The lung is fully re-expanded.

The administration of blood is, of course, imperative, and if properly matched blood is unobtainable, autotransfusion may be utilized.[13] An unhurried decision regarding the necessity for operation can usually be made if deflation is properly instituted and adequate blood is available for replacement. One can

make an accurate estimate of the rate of blood loss by observing the amount of blood being evacuated through the catheter, the degree of mediastinal displacement and the height of the fluid level in serial chest roentgenograms taken in the erect position, as well as recordings of the blood pressure and other clinical or laboratory data generally useful in estimating hemorrhage.

Published data indicate that operation should be seriously considered if the patient has lost more than 1000 cc. of blood or if bleeding has continued for twelve to twenty-four hours. The rate of the bleeding is an important consideration in weighing the indications for operation, and parallels between this disease and bleeding peptic ulcer can readily be drawn. An initial red-cell count of 2,500,000 or less[20] or blood loss and shock requiring transfusion of more than 500 cc. of blood every eight hours[21] appear to provide a convenient criterion for emergency operation.

All the patients thus far subjected to the emergency operation have tolerated the procedure remarkably well. The patient described above actually improved during operation, indicating that in these cases shock is corrected by operation. Delay in operation because of the patient's precarious condition must, for this reason, be vigorously resisted. Undue optimism regarding the prospects for spontaneous arrest of the bleeding must also be avoided. A decision for early operation is supported by a consideration of the small risk of thoracotomy, the probability that the treatment will be definitive and the rapid and complete recovery reported in all patients thus far operated on.[1,5,6,22] Early operation may also be favored because a late death can occur even after the hemorrhage has been arrested.[3] In addition delay in operation may permit the development of an organized hemothorax requiring the more extensive operation of pulmonary decortication.[2,6,7,22-25]

In making a decision to operate the surgeon faces a situation that closely parallels that of partial laryngeal obstruction, in which it has been said[26] that the time to perform the tracheotomy has arrived when the surgeon begins seriously to consider that such a procedure may be required.

Table 1 presents data in the case reported above and in 8 previously reported cases in which emergency thoracotomy was done for spontaneous hemopneumothorax.

We do not believe that the frequently cited fatal case reported by Hansen[4] should properly be included among thoracotomies for this indication. This patient had extensive bilateral cystic disease, and "hemorrhagic exudate" was only incidental to the spontaneous pneumothorax. Operation was undertaken fifteen days after onset to relieve dyspnea; death occurred from anoxia three days later.

TABLE 1. *Indications for and Results of Emergency Thoracotomy.*

Source	Date of Report	Age of Patient	Sex	Preoperative Management	Pathology	Source of Hemorrhage	Interval Between Onset and Operation	Blood Loss	Interval Between Operation and Discharge	Result
		yr.					*hr.*	*cc.*	*days*	
Myers et al.[3]	1951	22	M	Transfusion; thoracentesis.	Bleeding apical parietal adhesion	Apical adhesion	60	4410	11	Recovery
Ross[4]	1952	34	M	Transfusion; chest aspiration; catheter deflation.	Bleeding apical adhesion; bullae of lung.	Apical adhesion	Not recorded (probably 36)	"Large amount"	Not noted	Recovery
Beatty & Frelick[22]						Adhesions in apex & left costophrenic sinus		2700 cc. (plus large amount of clotted blood)		
Case 1	1952	33	M	Transfusion; deflation with needle.	Not recorded		72		10	Recovery
Case 2	1952	21	F	Transfusion; aspiration.	No source of air leak found; blebs, apex of lung.	Apical adhesions	40	1500	10	Recovery
Case 3	1952	33	M	Transfusion; aspiration.	Blebs, apex of lung	Apical pleura (adhesion?)	Less than 24	2400 cc. (plus moderate amount of fresh blood at operation)	12	Recovery
Borrie[5]										
Case 1	1953	21	M	Transfusion; aspiration.	Bullae, apex of lung; 1 ruptured.	Apical adhesion	Not recorded (about 30)	4000 cc. (plus "large clots")	15	Recovery
Case 2	1953	26	M	Aspiration	Ruptured apical emphysematous bullae	Ruptured emphysematous bleb, apex of lung	7	1100 cc. (plus "clots")	14	Recovery
Present case	1953	33	M	Transfusion; closed thoracotomy.	Blebs, apex of lung	Apical adhesion	120	3975*	11	Recovery

*Not included is approximately 500 cc. expelled through trocar during performance of closed thoracotomy.

Discussion

In this group of patients males predominated (hemopneumothorax in females is extraordinarily rare), and the average age was twenty-eight years. In addition to blood transfusions, preoperative aspiration was used in 5, continuous needle deflation in 1 and the more satisfactory subaqueous catheter deflation in 2 patients. At operation emphysematous blebs in the apex of the upper lobe were uniformly found, and with 1 exception the source of bleeding was the apical pleura (torn adhesion). The interval between onset and operation varied from seven hours to five days, and the reports demonstrate that in general there was an undesirable delay in operation. In 7 of the 8 cases, the patient's condition was one of unmistakable urgency, and a fatal outcome was probably avoided in each by operation. Hemorrhage for the most part was massive, and in the case reported above multiple transfusions amounted to substantially complete blood replacement. Recovery was rapid and complete in every case.

Measures to combat hemorrhagic shock and anoxia should be vigorously instituted during operation. In addition to a continuous transfusion of blood, a second infusion of dextrose and water, which permits an immediate shift to nor-epinephrine[27] is suggested. Assisted respiration, a minimal amount of anesthetic agent (ether is our preference) and rapid thoracotomy deserve mention. The patient's condition can dependably be expected to improve when blood and clots are evacuated from the pleural space and the lung is re-expanded. For this reason emphasis on rapid operation seems justified.

Summary and Conclusions

Operative experience with 8 previously reported cases of spontaneous pneumothorax associated with massive intrapleural hemorrhage is summarized, and an additional case is reported. Operative treatment of this grave condition has, thus far, been conducted without mortality. Suggestions for preoperative treatment and the indications and conduct of operation are considered. Early thoracotomy should be carried out in the treatment of this frequently fatal condition.

References

1. Borrie, J. Emergency thoracotomy for massive spontaneous haemopneumothorax. *Brit. M. J.* **2**:16-18, 1953.
2. Eidinger, S. L., and Rubin, E. H. Spontaneous pneumohaemothorax: report of 3 cases. *Canad. M. A. J.* **67**:43-46, 1952.
3. Jones, O. R., and Gilbert, C. L. Spontaneous haemopneumothorax. *Am. Rev. Tubere.* **33**:165-184, 1936.
4. Hansen, J. L. Spontaneous hemopneumothorax. *Acta med. Scandinav.* **122**:517-535, 1949.
5. Myers, R. T., Johnston, F. R., and Bradshaw, H. H. Spontaneous hemopneumothorax: report of case treated by thoracotomy. *Ann. Surg.* **133**:413-416, 1951.
6. Ross, C. A. Spontaneous hemopneumothorax. *J. Thoracic Surg.* **23**:582-592, 1952.
7. Fusia, D. A., Jr., and Cook, W. L., Jr. Spontaneous hemopneumothorax: review with report of 2 cases. *Am. Rev. Tubere.* **65**:744-753, 1952.
8. Moser, M. Spontaneous hemopneumothorax: treatment by early thoracentesis: report of 4 cases. *Dis. of Chest* **19**:339-345, 1951.
9. Solovay, J. Spontaneous hemopneumothorax: etiological considerations and case report. *Radiology* **53**:256-259, 1949.
10. Pitt, G. N. Case of rapidly fatal haemopneumothorax, apparently due to rupture of emphysematous bulla. *Tr. Clin. Soc. London* **33**:95-115, 1900.
11. Rolleston, H. D. Case of fatal haemopneumothorax of unexplained origin. *Tr. Clin. Soc. London* **33**:90-94, 1900.
12. Helwig, C., and Schmidt, E. C. H. Fatal spontaneous hemopneumothorax: review of literature and report of case. *Ann. Int. Med.* **26**:608-617, 1947.
13. Nalls, W. L., and Matthews, J. H. Idiopathic spontaneous hemopneumothorax: evaluation of its treatment and report of 3 cases. *Dis. of Chest* **18**:612-623, 1949.
14. Towson, R. T. Spontaneous pneumo-haemothorax. *Canad. M.A.J.* **70**:188, 1954.
15. Hyde, L., and Hyde, B. Benign spontaneous hemopneumothorax. *Am. Rev. Tubere.* **63**:417-426, 1951.
16. Best, C. H., and Taylor, N. B. A. *The Physiological Basis of Medical Practice: A University of Toronto text in applied physiology.* Second edition. 1872 pp. Baltimore: Wood, 1939. P. 572.
17. Hartzell, H. C. Spontaneous hemopneumothorax: report of 3 cases and review of literature. *Ann. Int. Med.* **17**:496-510, 1942.
18. Hughes, F. A., Jr., Kraeft, N. H., and Lowry, C. C. Treatment of idiopathic spontaneous pneumothorax. *J.A.M.A.* **146**:244-247, 1951.
19. Williams, M. H. Discussion of Rockey, E. E. Care of thoracic and thoracoabdominal wounds in combat zone in Korea. *J. Thoracic Surg.* **24**:435-456, 1952, and Vallee, A. R. Management of war wounds of chest. *Ibid.* **24**:457-481, 1952.
20. Stewart, J. D., Scheer, S. M., Potter, W. H., and Masower, A. J. Management of massively bleeding peptic ulcer. *Ann. Surg.* **128**: 791-802, 1948.
21. Dunphy, J. L., and Hoerr, S. O. Indication for emergency operation in severe hemorrhage from gastric or duodenal ulcer. *Surgery* **24**:231-238, 1948.
22. Beatty, G. A., and Frelick, R. W. Hemopneumothorax: reïvaluation of treatment. *Ann. Int. Med.* **36**:845-851, 1952.
23. Elrod, P. D., and Murphy, J. D. Spontaneous hemopneumothorax treated by decortication: case report. *J. Thoracic Surg.* **17**:401-407, 1948.
24. Seley, G. P., and Neuhof, H. Pulmonary decortication for clotted hemothorax following idiopathic spontaneous hemopneumothorax. *J. Thoracic Surg.* **21**:600, 1951.
25. Williams, M. H. Technique of pulmonary decortication and pleurolysis. *J. Thoracic Surg.* **28**:652-664, 1950.
26. Lahey, F. H., and Hoover, W. B. Tracheotomy after thyroidectomy. *Ann. Surg.* **133**:63-76, 1951.
27. Deterling, R. A., Jr., and Apgar, V. Use of nor-epinephrine (l-arterenol) as pressor drug with special reference to thoracolumbar sympathectomy. *Ann. Surg.* **133**:37-43, 1951.

MYOCARDIAL RUPTURE AND HEMOPERICARDIUM ASSOCIATED WITH ANTICOAGULANT THERAPY*

A Post-Mortem Study

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BOSTON

A DISTURBING feature of the occasional case of fatal hemopericardium following anticoagulant therapy for myocardial infarction is the absence of an obvious explanation for the hemorrhage. Heretofore, a pericardium distended with blood in a patient with myocardial infarction has usually been the result of a ruptured myocardium. However, Hammarsten[1] reported in 1949 a case with massive hemopericardium that followed Dicumarol treatment in which low levels of prothrombin activity (10 per cent or less) were obtained; 800 cc. of blood was found in the pericardium and yet no rupture of the heart or a vessel could be demonstrated. Nichol,[2] Goldstein and Wolff,[3] Syner[4] and Anderson, Christensen and Edwards[5] later reported similar cases. Rose, Ott and Maier[6] described a patient with acute myocardial infarction whose prothrombin time reached 84 seconds on anticoagulant therapy. Cardiac tamponade developed and the patient was in extremis but recovered after the removal of 700 cc. of bloody fluid by pericardiotomy.

A recent editorial[7] states that in the original study of the Committee on the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction "hemopericardium was found in 11 of the treated and only four of the control group." More recently, Russek and Zohman,[8] from a survey, found 122 deaths attributed by the attending physician to anticoagulants; 20 of these were due to hemorrhagic pericarditis.

Experimentally, Quick, Honorato and Stefanini[9] demonstrated that heart puncture in a rabbit with reduced prothrombin activity caused fatal hemopericardium. If the prothrombin time exceeded 24 seconds (normal, 6 seconds), fatal hemorrhage into the pericardium occurred; if the prothrombin time was less than 19 seconds the animal survived. On the other hand, Blumgart et al.[10] found no increase in hemorrhage or hemorrhagic pericarditis in dogs with experimentally produced myocardial infarction given anticoagulants.

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POST-MORTEM DATA

To evaluate the possible effect of anticoagulants on the frequency of hemopericardium in patients dying with myocardial infarcts, the autopsy protocols of the Massachusetts General Hospital from 1932 through 1951 were reviewed. If blood or bloody fluid was described as being within the pericardium the case was reviewed in more detail to determine a cause for the hemopericardium other than the infarct or its sequelae. All cases were excluded from this study in which there was clinical or post-mortem evidence of trauma to the heart, including ante-mortem, agonal or post-mortem needle punctures, blood dyscrasias, uremic pericardial involvement by carcinoma, bacterial endocarditis or aneurysm ruptured into the pericardium. Those with hemopericardium due to rupture of infarcted myocardium are analyzed separately.

Among 8852 autopsies there were 955 cases with myocardial infarction. Three hundred and thirteen were recent (less than six weeks old), an additional 232 had areas of infarction both recent and old, and 410 were old. For consideration, therefore, are 545 cases with areas of recent infarction, 79 of which were associated with hemopericardium.

Because anticoagulants were first used in 1946 to prevent complications of myocardial infarction, the 79 cases of hemopericardium were divided into two main groups: those occurring between 1932 and 1945 (Period 1) and those between 1946 and 1951 (Period 2). Period 2 cases were further divided into patients who received anticoagulants and those who did not; the latter group may serve as controls regarding over-all better treatment of patients in recent years and possible variables.

For the purpose of this study a prothrombin activity of 10 to 30 per cent was considered as in the therapeutic range. An activity less than 10 per cent was regarded as excessive, and pertinent if it occurred within ten days of death. If heparin was used, a clotting time of 30 to 60 minutes was accepted as within the therapeutic range; above 60 minutes was excessive. Sixty-four patients received Dicumarol, 5 received heparin and Dicumarol, and 2 received Tromexan alone.

The data (Table 1) indicate that the incidence of hemopericardium with or without myocardial rupture was not significantly different during Periods 1 and 2 in the patients who did not receive anticoag-

ulants. There is, however, at least a threefold rise in the prevalence of hemopericardium without rupture and a twofold increase of rupture in the patients who received anticoagulants over those who did not in both Periods 1 and 2. By the chi-square test the probability that this difference occurred by chance was less than .100.

One of the anticoagulant-treated cases resembles those previously described.[1-5] The patient was given Dicumarol, the prothrombin concentration reached a level below 10 per cent, and death resulted from a massive hemopericardium. No source for the bleeding besides the infarct was found. Another patient treated with Dicumarol, with prothrombin levels maintained in a therapeutic range, died from tamponade. Hemorrhage occurred from a coronary artery that ruptured at the site of the thrombus.

The frequency of hemopericardium increased as the anticoagulant effect increased. When the anticoagulant effect was less than that desired — that is, less than therapeutic levels — 7 of 28 (25 per cent) had hemopericardium; at therapeutic levels, 11 of 32 (34.4 per cent) had hemopericardium, and with excessive anticoagulant effect 6 of 11 (54.5 per cent)

TABLE 1.

GROUP	CASES WITH INFARCTS	CASES WITH HEMOPERICARDIUM			
		TOTALS	WITHOUT RUPTURE	WITH RUPTURE	
Period 1 (1932-1945)	233	32	14	6.0%	18	7.7 %
Period 2 (1946-1951): Without anticoagulants	241	23	11	4.6%	12	4.98%
With anticoagulants	71	24	14	19.7%	10	14.1 %

had hemopericardium. The differences are striking, but the groups are too small to be statistically significant.

The time elapsed between the onset of symptoms of myocardial infarction and rupture in anticoagulant-treated patients was no different from that in those not receiving anticoagulants. Mural thrombi were present in 17 (56.7 per cent) of 30 patients who had ruptured ventricular wall and were not treated with anticoagulants; 6 (60 per cent) of 10 treated patients had mural thrombi, and 5 of these had therapeutic or excess anticoagulant effect. Of the 40 patients with ruptured hearts 20 were hypertensive. In this latter group there was no significant difference between those receiving Dicumarol and those not so treated.

DISCUSSION

Despite the increased frequency of hemopericardium there is only 1 case in this series of hemorrhagic pericarditis with tamponade without rupture in which the anticoagulants may be regarded as responsible for the fatal outcome. Except for this case and for the case with the ruptured coronary artery cited above, all anticoagulant-treated cases with fatal hemopericardium were the result of rupture of infarcted myocardium. The increased occurrence of bloody fluid in the treated patients in this group is not alarming unless one considers what this may portend. Would tamponade ultimately have developed if these patients had survived a longer time?

The prevalence of myocardial rupture in acute myocardial infarction was significantly higher in the anticoagulant-treated cases than in the others. If myocardial rupture does begin as a small tear in infarcted muscle, with diminished coagulation of the blood, prompt sealing of this defect would be less likely to occur, and rupture would seem more probable. However, this theory is not supported by our findings, for mural thrombi were not prevented; they occurred at the same rate in both anticoagulant-treated and untreated patients, and rupture occurred despite their presence.

Since these data are obtained entirely from autopsy material they are weighted by fatal cases and obviously do not take into account the desirable effects of anticoagulant treatment. It does not appear from review of the clinical records that there was any selection of patients for anticoagulant therapy, and we do not believe that selection was a factor in the results obtained. Since early ambulation or chair treatment of coronary thrombosis was not being practiced, this was not a factor. This study does corroborate the suspicion that a certain risk is involved in diminishing the normal coagulability of the blood in patients with myocardial infarction. The risk may be small and is possibly far outweighed by the advantages of this method; further reviews of this type will give an idea of the magnitude of the risk.

SUMMARY AND CONCLUSIONS

From a review of post-mortem data, the rate of cardiac rupture in patients dying with acute myocardial infarction was higher in those on anticoagulant therapy.

Hemopericardium in the absence of myocardial rupture occurred with greater frequency in the anticoagulant-treated patients, but there was probably little effect on mortality.

Anticoagulant therapy of acute myocardial infarction carries a risk as well as possible advantages under proper circumstances.

Since this paper was submitted for publication the final report of the Committee on Anticoagulants of the American Heart Association has been published.[11] Their experience with hemopericardium and cardiac rupture, although consisting of a smaller number of autopsied cases, correlates fairly closely with ours. The following table based on their findings is presented for comparison with Table 1.

GROUP	NO. OF AUTOPSIES	CASES WITHOUT RUPTURE	CASES WITH RUPTURE
Without anticoagulants	48	2 (4.2%)	4* (8.3%)
With anticoagulants	41	5 (12.2%)	8 (19.5%)

*Three of these were septal ruptures without hemopericardium.

They conclude as follows (italics theirs):

It seems safest, therefore, to base their clinical practice on the expectation that anticoagulants may increase somewhat the frequency and severity of hemorrhage, particularly intracardiac hemorrhage and may increase the risk of myocardial rupture and hemopericardium with cardiac tamponade. Alertness on the part of the clinician and good management of anticoagulant therapy can minimize these risks. Therefore the physician using anticoagulants should not only supervise such therapy with care but also should be equipped for the clinical recognition and treatment of cardiac tamponade and other hemorrhages both in and outside the heart.

References

1. Hammarsten, J. F. Hemopericardium without rupture of heart following Dicumarol therapy for myocardial infarction. *Minnesota Med.* **32**:1003, 1949.
2. Nichol, E. S. Risk of hemorrhage in anticoagulant therapy. *Ann. West. Med. & Surg.* **4**:71-81, 1950.
3. Goldstein, R., and Wolff, L. Hemorrhagic pericarditis in acute myocardial infarction treated with bishydroxycoumarin. *J.A.M.A.* **146**:616-621, 1951.
4. Syner, J. C. Extensive pericarditis complicating myocardial infarction. *U. S. Armed Forces M. J.* **3**:698-708, 1952.
5. Anderson, M. W., Christensen, N. A., and Edwards, J. E. Hemopericardium complicating myocardial infarction in absence of cardiac rupture: report of 3 cases. *Arch. Int. Med.* **90**:634-645, 1952.
6. Rose, O. A., Ott, R. H., Jr., and Maier, H. C. Hemopericardium with tamponade during anticoagulant therapy of myocardial infarct: report of case with recovery following pericardiotomy. *J.A.M.A.* **152**:1221-1223, 1953.
7. Editorial. Anticoagulants as cause of hemorrhage. *J.A.M.A.* **144**: 1466, 1950.
8. Russek, H. I., and Zohman, B. L. Anticoagulant therapy in acute myocardial infarction: survey of specialists' opinions concerning indications, results and dangers. *Am. J. M. Sc.* **225**:8-13, 1953.
9. Quick, A. J., Honorato, R., and Stefanini, M. Value and limitations of coagulation time in study of hemorrhagic diseases. *Blood* **3**:1120-1129, 1948.
10. Blumgart, H. L., Freedberg, A. S., Zoll, P. M., Lewis, H. E., and Wessler, S. Effect of Dicumarol on heart in experimental acute coronary occlusion. *Am. Heart J.* **36**:13-27, 1948.
11. Wright, I. S., Marple, C. D., and Beck, D. F. *Myocardial Infarction: Its clinical manifestations and treatment with anticoagulants: A study of 1031 cases.* 656 pp. New York: Grune and Stratton, 1954. Pp. 392-455.

SPECIAL ARTICLE

PARENS PATRIAE

The Sovereign Power of Guardianship

C. C. Cawley

SHARON, MASSACHUSETTS

MARK Twain, vacationing in the mountains near Vienna, one evening fell over a 75-foot cliff. He lay at the bottom, "an incoherent series of compound fractures," until he was by good luck "found by some peasants who had lost an ass." These carried him to the nearest farmhouse and summoned the only available aid, a lady from Boston, summering nearby, who was a "Christian Science doctor." She sent back word that there was nothing the matter with him, that his pains were a delusion, that she would now give him "absent treatment" and that she herself would come in the morning. After the lady's visit Mark Twain in desperation engaged a horse doctor, who after horse-wise diagnosis applied "energetic measures" and restored him to health.[1]

One cold winter evening of that same period, a friend of mine, then a boy, with a chum "iced" a sled run on their New England hillside. The following morning the friend's first wild descent ended with a crash and a broken leg. After helping to carry him home my friend returned to his own home, where he reported to his parents how his companion's father, a Christian Scientist, had refused his offer to run for a doctor, and instead was "demonstrating" over the boy, who lay on his bed screaming with pain. My friend's father, enraged, enlisted two sizeable neighbors and a doctor. They entered the boy's house, and, while the others held the father prisoner downstairs, the doctor went upstairs and properly set the boy's leg. This done, the party marched out again.

Granted that Mark Twain, *sui juris,* — in his own right, — was free to submit himself at his own risk to any mode of ministration he chose and granted that society did not then, and does not now, countenance the forthright action of my friend's father, still, regarding children's welfare, the state in its role of *parens patriae* firmly asserts its right to interfere to some extent with the rights of parenthood and of religion. It is well established that a parent who, owing to religious conviction, denies his sick child necessary medical aid commits a misdemeanor, and that, if the child consequently dies, the parent is liable for manslaughter.

Rubenstein[2] lists the leading English, Canadian and United States decisions on this point as follows: *Reg. v. Senior* (1899), in which a father, a member of the faith-healing "Peculiar People," was convicted of manslaughter after his nine-month-old infant died of diarrhea and pneumonia without medical care (7 of his 12 children had already died under similar circumstances[3]); *Rex v. Lewis* (1903), in which a Christian Scientist father was convicted of manslaughter after his six-year-old son, treated only by a "demonstrator," died of diphtheria[4]; and *People v. Pierson* (New York, 1903), in which a father, a member of the faith-healing "Christian Catholic Church," was convicted of a *misdemeanor* after his sixteen-month-old daughter died of catarrhal pneumonia after a month of whooping cough, all the time without medical care. As often noted the record in this case shows all the elements necessary for a manslaughter conviction to have been clearly present.[5]

But what satisfaction is it to society to punish the father after the child is dead? Even the cruel God of Israel, after testing Abraham's faith, stopped him from sacrificing his son Isaac.[6] Must civilized men,

today, look helplessly on until after a fanatical parent has completed the sacrifice of his innocent child upon the altar of his religion?

Rhoda and Darrell Labrenz had been childhood sweethearts in Dalton, Wisconsin. Around 1950 they joined the Jehovah's Witnesses sect and with their first child, Kit, moved to Chicago. Cheryl Linn was born in Bethany Hospital on April 11, 1951. It soon appeared that Cheryl had an Rh blood condition that threatened her life, but her mother, twenty-year-old Rhoda Labrenz, refused to consent to a blood transfusion:

> We feel that we would be breaking God's commandment, also destroying the baby's life for the future, not only this life, in case the baby should die and breaks the commandment, not only destroys [*sic*] our chances but also the baby's chances for future life. We feel it is more important than this life.

Dr. Herman N. Bundesen, health commissioner for the city of Chicago, called in the child's father, Darrell (who was twenty-five years of age), and warned him of the seriousness of the child's plight and of the need for immediate action. The reply was as follows[7]:

> The sanctity of the blood is a thing we cannot tamper with. Everybody knows that blood is the life force and we do not have control of life. Only Jehovah has that. Transfusion, which is a form of drinking or eating blood, is forbidden to us who are Jehovah's Witnesses.[8]

Tuesday noon, April 17, a conference was held in the Family Court with the first assistant State's Attorney, the head of the Brief Department, the chief administrator of the Family Court and others. The problem was to decide what action could be taken and how quickly to prevent what seemed to be the inevitable death of six-day-old Cheryl Linn in a few hours.

The statutes were examined. Section 95 of the Criminal Code makes it unlawful for any person having the care or custody of any child willfully to cause or permit the child to be injured or placed in such a situation that its life or health may be endangered. The Family Court Act provides (Section 95) that the court may, when the health or condition of any child found to be dependent, neglected or delinquent requires, order the guardian to place the child in a public hospital or institution, which will receive it for like purposes, without charge to the public authorities. As against this, Article II, Section 3 of the Illinois Constitution of 1870 provides that "the free exercise and enjoyment of religious profession and worship, without discrimination, shall forever be guaranteed." It was believed that if action was forced a constitutional defense would be interposed. Still, the same section of the Constitution provides, "But the liberty of conscience hereby secured shall not be construed to dispense with oaths or affirmations, excuse acts of licentiousness, or justify practices inconsistent with the peace or safety of the State."

The course decided upon was that a petition should be filed in the Family Court alleging the child to be dependent because she was without proper parental care and guardianship, and to set a hearing for the following morning. A probation officer quickly prepared the petition. The State's Attorney placed a squad car and a police officer at his disposal until all persons concerned had been located and served. At 4 o'clock he returned the completed summons to the clerk's office. A subpoena was served on the attending physician at the hospital. The Health Commissioner was notified. Nothing more could be done.

At the opening of court on the following morning, Darrell and Rhoda Labrenz, red-eyed and distraught, each with a Bible in hand, sat in the second row facing the Honorable Robert Jerome Dunne, presiding judge of the Family Court. The case had been given wide publicity in every local newspaper; a battery of cameras and sound recorders was set up, and reporters swarmed outside the courtroom. The matter was promptly called up for hearing. Motions for a continuance and for dismissal as contrary to the Constitution were taken under advisement. The trial proceeded.

A health-department pediatrician gave his expert conclusion: "Without a transfusion, I will say absolutely, this child cannot live; or, if it should, could not live without permanent brain injury." His chief, Health Commissioner Herman Bundesen, backed him up: "The one chance this baby has is to get a transfusion." Another expert testified that the child's red-cell count had dropped from the normal 5,000,000 at birth to 1,950,000 and added, "Time is being lost now. There cannot be any further delay."

To each parent the state's attorney put only one question: "Will you now agree to a transfusion?" Both refused. "My religious teachings forbid it," the father said adamantly.[9]

At the conclusion of the hearing, which took less than an hour, the motions under advisement were overruled. Colonel Harry Hill, chief probation officer, was appointed guardian, with the right to consent to necessary blood transfusions. An emergency ambulance was waiting at the courthouse. The transfusion apparatus had already been set up at Michael Reese Hospital. There, not a minute was wasted in giving 60 cc. of blood to Cheryl. Within forty-eight hours her red blood cells seemed to be winning the battle. She continued to improve. Within three days she was out of danger.

On May 4 the State presented a further petition to Judge Dunne, mentioning the infant's improved condition and asking for a modification of the guardianship order. After the hearing an order was entered retaining guardianship but releasing Cheryl from the hospital into the custody of her parents, with the provision that the child was to be examined by a doctor every two weeks until June 15, when the judge promised to inquire into the facts again and to make whatever further orders were necessary. At home Cheryl continued to make progress. Medical reports submitted to the judge at the two subsequent hear-

ings were even more reassuring. On June 29 a final order was entered releasing Cheryl Linn from guardianship.

The case was brought to the Supreme Court of Illinois on a writ challenging the propriety of the action of the Family Court of Chicago — that is, the circuit court of Cook County — on constitutional grounds. The Court first of all ruled against the State's contention that the case was now moot and should be dismissed because the blood transfusion had been administered, the guardian discharged and the proceedings dismissed. Although recognizing this general rule the Court pointed out that a well recognized exception exists when the issue presented is of substantial public interest.

> We find that the present case falls within that highly sensitive area in which governmental action comes into contact with the religious beliefs of individual citizens. Both the construction of the statute under which the trial court acted and its validity are challenged. In situations like this one, public authorities must act promptly if their action is to be effective, and although the precise limits of authorized conduct cannot be fixed in advance, no greater uncertainty should exist than the nature of the problems makes inevitable. In addition, the very urgency which presses for prompt action by public officials makes it probable that any similar case arising in the future [one did arise, in January, 1954] will likewise become moot by ordinary standards before it can be determined by this court. For these reasons, the case should not be dismissed as moot.

Did the lower court lack jurisdiction because the child was not a "neglected" or "dependent" child within the meaning of the statute?

> So far as here pertinent, the statute defines a dependent or neglected child as one which "has not proper parental care." The record contains no suggestion of any improper conduct on the part of the parents except in their refusal to consent to a blood transfusion. And it is argued that this refusal on the part of the parents does not show neglect, or a lack of parental care. Neglect, however, is the failure to exercise the care that the circumstances justly demand. It embraces willful as well as unintentional disregard of duty. It is not a term of fixed and measured meaning. It takes its content always from specific circumstances, and its meaning varies as the context of surrounding circumstances changes. The question here is whether a child whose parents refuse to permit a blood transfusion, when lack of a transfusion means that the child will almost certainly die or at best will be mentally impaired for life, is a neglected child. In answering that question it is of no consequence that the parents have not failed in their duty in other respects. We entertain no doubt that this child, whose parents were deliberately depriving it of life or subjecting it to permanent mental impairment, was a neglected child within the meaning of the statute. The circuit court did not lack jurisdiction.

Were the parents merely exercising their right to avoid the risk of a proposed hazardous operation, a choice not indicative of a lack of proper parental care? To this proposition the Court gave a short answer: "The facts here disclose no such perilous undertaking, but, on the contrary, an urgently needed transfusion — virtually certain of success, if given in time — with only such attendant risk as is inescapable in all the affairs of life."

Does the Juvenile Court Act, as held to be applicable, deprive the parents of freedom of religion and of their rights, as parents, in violation of the Fourteenth Amendment to the Constitution of the United States and of section 3 of article II of the Constitution of Illinois?

> Because the governing principles are well settled, this argument requires no extensive discussion. Concededly, freedom of religion and the right of parents to the care and training of their children are to be accorded the highest possible respect in our basic scheme. But "neither rights of religion or rights of parenthood are beyond limitation" [quoting *Prince v. Mass.* and referring to *Reynolds v. U.S.* and *Jacobson v. Mass.*]. Indeed, the early decision in the Reynolds case, upholding a Mormon's conviction for bigamy against the defense of interference with religious freedom as guaranteed in the first amendment, leaves no doubt about the validity of the action here taken. The following language of that opinion is of particular interest: "Laws are made for the government of actions, and while they cannot interfere with mere religious belief and opinions, they may with practices. Suppose one believed that human sacrifices were a necessary part of religious worship, would it be seriously contended that the civil government under which he lived could not interfere to prevent a sacrifice? Or if a wife religiously believed it was her duty to burn herself upon the funeral pile of her dead husband, would it be beyond the power of the civil government to prevent her carrying her belief into practice?"

Finally, did the trial court commit prejudicial error in excluding from evidence the religious magazine, *Awake?*

> The contention is without merit. Except as it might bear upon the good faith of the parents' belief in the Scriptural prohibition against blood transfusion, it was inadmissible as hearsay. And since the sincerity of the parents' religious beliefs was not questioned, the exclusion of the magazine was not error.

The Court accordingly affirmed the judgment of the circuit court of Cook County.[10]

That was in November, 1951. Afterward, a petition was filed for a writ of certiorari in the United States Supreme Court returnable to the October, 1952, term of the Court. On October 13, 1952, the Family Court was notified by the clerk of the Supreme Court in Washington that the writ had been denied. And so it ended.

Janet Lynn Morrison, the day after she was born in Kansas City, in 1952, showed symptoms of erythroblastic anemia, with extreme jaundice and a perilously dropping blood count. There was no known remedy except blood transfusions, for which her Jehovah's Witness father refused consent. A complaint accordingly was filed in Juvenile Court, and the Labrenz type of procedure afterwards followed. On appeal the Missouri court reaffirmed the stand of the Illinois Supreme Court. Regarding the child's right to life, the court went back to cite the Declaration of Independence, and concerning the state's rightful role of *parens patriae* went back a great deal farther and quoted Aristotle.[11]

On January 14 and 15, 1954, papers across the country carried the story of Chicago's second Jehovah's Witness case. Thomas Grzyb, Jr., was born there on January 6, with a very serious throat condition. The

father, Thomas Grzyb, twenty years of age, when told that his baby's life depended upon immediate blood transfusions, said "Our belief won't allow it. It's better to have a dead baby without the blood than a living baby with the transfusion." At a preliminary hearing on January 13, the Grzybs were urged by the judge, because of the baby's critical condition, to waive their legal right to delay the full hearing by one day. They refused. "If the baby dies," said the eighteen-year-old mother, Barbara Grzyb, "that is God's will. I have no fear. The blood won't make any difference. I am not going to hand him over to the court until I have to. The judge doesn't care what's in the Bible."[12] There was no alternative to setting the hearing for the following morning. And that night, just after midnight, the baby died. Said Thomas Grzyb, afterward, "We want more children. But if such a thing happens again, and if I am called a murderer, that is God's will. I am sorry the child died. But if it is God's will that a life be taken, it must be taken."[13] No criminal action was brought against the parents. What was the use?

In none of these 3 cases was "faith healing" involved. The parent was not attempting to employ some substitute for medical skill in an effort to save the child's life. Indeed, these cases uniformly demonstrate an incredible disregard for the life of the child, an utter determination to adhere to a religious commandment regardless of whether the child lives or dies. It does not appear to be an outrageous violation of civil rights and "freedom of conscience" for the state to have police power to declare such a child neglected and thus to save its life. It was well said, in a recent case concerning distribution of religious pamphlets by a Jehovah's Witness child:

> The right to practice religion freely does not include liberty to expose the community or child to communicable disease or the latter to ill health or death . . . Parents may be free to become martyrs themselves. But it does not follow they are free, in identical circumstances, to make martyrs of their children before they have reached the age of full and legal discretion when they can make that choice for themselves.[14]

I am happy to be able to append some information just received that today Cheryl Linn Labrenz is living a normal life with her parents, and is a fine, healthy child.

References

1. Clemens, S. (Mark Twain). *Christian Science: With notes containing corrections to date.* 362 pp. New York: Harper, 1907. (The chapters containing this account first appeared in 1899 in *Cosmopolitan* magazine.)
2. Rubenstein, I. H. Criminal aspects of faith healing. *New Eng. J. Med.* **224**:239-242, 1941.
3. *Reg. v. Senior* (1899) 1 Q. B. 283, 19 Cox, C. C. 219.
4. *Rex v. Lewis* (1903) 6 Ont. L. Rep. 132, 1 B. R. C. 732.
5. *People v. Pierson* (1903) 176 N. Y. 201, 68 N. E. 243. (Note: The subject is well covered in 10 A. L. R. 1129-1152.)
6. *Genesis* **22**:12.
7. *Time*, April 30, 1951.
8. "Flesh with the life thereof, which is the blood thereof, shall ye not eat." *Genesis* **9**:4.
9. *Bangor* (Me.) *Daily News*, April 18, 1951.
10. *People ex. rel. Wallace v. Labrenz*, 411 Ill. 618, 104 N. E. 2d 769 (1952).
11. *Morrison v. State* (Mo. Ap.) 252 S. W. 2d 97 (1952).
12. *Boston* (Mass.) *Traveler*, January 14, 1954.
13. *Springfield* (Mass.) *News*, January 14, 1954.
14. *Prince v. Mass.* (1944) 321 U. S. 158, 167, 64 S. Ct. 438, 88 L. Ed. 645.

MEDICAL PROGRESS

EPILEPSY (Concluded)

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BOSTON

Acetylcholine. The presence of acetylcholine within nerve cells is generally accepted as essential for the propagation and synaptic transmission of nerve impulse in most of the peripheral nervous system. Also, many accept this role for acetylcholine in the brain. The chemical is thought to affect the permeability of the cell membrane separating the high intracellular potassium concentrations from the high extracellular sodium concentrations. More specifically, free acetylcholine is thought to foster membrane repolarization and to restore the intracellular and extracellular ionic concentration gradients that have been neutralized during the transmission of a nerve impulse.[17] Excessive amounts of free acetylcholine applied to the cortex induce epileptic activity.[4] A major portion of acetylcholine in the cell is present in the "bound" or inactive form. The "free" or active form with which it is in dynamic equilibrium is rapidly destroyed by the enzyme cholinesterase.[16]

Potassium. In nerve tissue, high concentrations of potassium are maintained within the cell by an active process that requires energy (as pointed out below). Escape of intracellular potassium ions accompanies the passage of nerve impulse.[18] Increasing the concentration of potassium or decreasing that of sodium outside the cell diminishes neuronal excitability, regardless of the manner in which the concentration gradients are lowered. Colfer and Essex demonstrated that a redistribution of electrolytes of cerebrocortical neurons with a decrease of potassium and an increase of sodium followed experimentally induced seizures in animals.[16]

Glutamic acid. Terner, Eggleston and Krebs[19] found that glutamic acid or its derivatives, glutamine, gamma-amino-butyric acid and aspartic acid can be

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converted to the corresponding keto-acids (alpha-ketoglutaric or oxaloacetic) in the basic energy-producing cycle of the cells, or, conversely, they may be augmented from these sources. Participation of glutamic acid in these energy-producing cycles permits it to transport potassium across the cell membrane against a concentration gradient — that is, to "recharge" the cell.

A better known function of glutamic acid in the form of its amide, glutamine, is the storage and transport of ammonia, an increased production of which occurs during nerve activity.[20,21]

Glutamic acid derivatives are probably active also in protein buildup and repair within the cell.[21]

Tower's studies, then, have added to the functions of glutamic acid, an essential part in the metabolism of acetylcholine.[16,21]

In view of these considerations, Tower concludes that glutamic acid metabolism occupies a central position in the interactions between the carbohydrate energy-producing cycles and amino acid metabolism in the central nervous system. Because the brain depends almost exclusively on carbohydrate sources of energy and because alternate metabolic pathways for energy production found in other tissues apparently do not exist in the brain, *interference with the cycle at any stage* could upset the balance of the entire system.[22]

Clinical application. Tower had demonstrated the existence of an acetylcholine binding deficiency in epileptic cortex in the laboratory. He had found that glutamine paralleled and exceeded anticonvulsant drugs in its ability to correct this defect. The next step was to test the effect of glutamine in epileptic patients. Before the American Academy of Neurology in May, 1954, Tower[22] reported encouraging clinical and electroencephalographic results in several patients treated with glutamine and its close chemical relative, asparagine. Because both these substances are now prohibitively expensive, a large-scale trial of their effectiveness has not yet been possible.

Neurophysiology

This is a subject of deep interest and wide significance for the understanding of epilepsy. The human brain is the most intricate and the most wonderful of all the creations of God. Better realization of how this organ functions so that misfunction can be corrected is important not only for epilepsy but for all diseases based on brain disorder. Research of the recent past has opened fresh and promising areas of understanding and treatment. Clinicians and neurophysiologists of many lands are searching feverishly for new facts. An account of many investigations appears in books and journals mentioned in the first section of this report.

Tracings of the electric potentials derived from the scalp, cortex and depths of the brain disclose that seizure discharges may remain localized in the superficial feltwork of the cortex without involving the neurons lying in deeper layers. Microelectrodes have been placed in individual cells, a technic that may throw light on why neurons become epileptogenic. Simultaneous recordings are made from as many as 25 localizations upon or within the brain. Toposcopic display systems that show the spread of fluctuating potentials projected over a cathode-ray screen give information about both frequency and phase. Direct as well as alternating currents can be studied. Automatic frequency analyzers are new tools in the hands of students of the brain.

Rhythm is a mystery of nature. Epilepsy is dysrhythm. How can one explain the apparently inherent automatic rhythm of the electric waves of the brain? The autorhythmicity is influenced by chemicals such as acetylcholine and Metrazol that excite or drugs like cocaine that depress. Cells maintain rhythmic activity even when isolated from all neuronal connections; yet the excitability of cortical cells is dependent on many corticopetal pathways.

Another important property of epileptic electric activity is its tendency to move from its site of origin. This spread of afterdischarge travels along neuronal pathways only. Some are constantly in use; others are put in action by certain unphysiologic processes. In man the spread of discharge along specific circuits may be facilitated and "sensitized" so that all subsequent discharges in the general area tend to follow the same course. Penfield's[4] pioneering observations at the operating table have suggested that a similar process may occur in epileptic patients. If a certain point of the cortex is stimulated, especially if this is close to an epileptogenic lesion, the externally applied electric impulse finds its way into channeled circuits and reproduces for the patient some complex aura such as a psychologically traumatic scene or recalls to him some tune.

Despite the evidence cited above, the possibility of some extraneuronal spread of epileptic discharge has not been ruled out. An example of this is the so-called "spreading depression" observed in the brain of an animal. This creeps across the cortex by contiguity without discrimination for structural barriers. Although this is generally attributed to physical artifact of the exposed cortex, possibly a clinical counterpart is a patient's account of a very slow spread of sensation or motion.

Correlation of a symptom, a brain-wave pattern and a cerebral locus is a crucial problem of epilepsy research. The distinctive pattern of the bilaterally synchronous, 3 per second alternate spike and wave discharge and its coincidence with a brief period of blank unconsciousness makes this pattern a key witness in attempts to identify the long-searched-for site of consciousness. In 1947 Penfield and Jasper[4] applied a 3 per second electric stimulus to thalamic areas (massa medialis) of cats and obtained coincidentally a spike-wave recording from the animal's cortex, a reproduction of that observed during the petit-mal

seizure of patients. In support, Gastaut observed that seizures associated with focal cortical lesions are less susceptible to photic and Metrazol activation than seizures associated with bilateral spike-wave discharges.

However, the Gibbses and others find that spike-wave discharges may appear in the cortex of a petit-mal patient at a time when they are absent from subcortical structures. Williams has evidence also that the slow wave originates in the thalamus and the spike in the cortex. Cortical stimulation of the cingulate gyrus of animals by Margaret Lennox caused a self-perpetrating 3 per second spike wave afterdischarge. Intracortical application of fluoroacetate causes the petit-mal type of discharge in dogs. Metrazol introduced into the arterial blood stream causes spike-wave discharges to appear if the blood goes to the cortex but not if it goes to the central gray mass. The discharges follow topical application of Metrazol to the cortex and are not prevented by severe damage to the thalamus. Petit-mal attacks are not a concomitant of thalamic tumors. Obviously, the spike and wave complex is ubiquitous and requires additional study.

The Reticular System

A central problem of brain function concerns the neurophysiology of consciousness and awareness. An episode of impaired consciousness or awareness is the simplest manifestation of metabolic epilepsy; hence, information that links function and location is eagerly sought.

In August, 1953, the Council for International Organizations of Medical Sciences sponsored a symposium in Montreal. Brazier has summarized the contributions (to be printed by Charles C Thomas under the title, "Brain Mechanisms and Consciousness").

Reticular means "net." The brain-stem reticular system is also termed "central internuncial system" and corresponds to Penfield's "centrencephalic system." Gray masses to the number of 98 can be distinguished in the lower brain stem. Stimulation of the system causes generalized electroencephalographic changes and arouses a sleeping animal, whereas destruction of the cephalad portion results in chronic coma (Magoun). Activity of neurons in the ascending reticular system is essential for maintenance of the waking stage, and fluctuations in the activity are reflected as changes in the level of consciousness. Cortical control of the waking state invokes the phenomenon of voluntary attention (Bremer). Sensory impulses reach their specific cortical receiving areas at all times, even during inattentiveness, sleep, coma and anesthesia. The reticular system is a meeting ground for signals from all receptors; hence, for attention, a selection of signals is necessary. The reticular system may perform that editing process and may also itself reinforce specific signals, win the neurons for its own purpose and thus break the intrinsic rhythm of the cortex — thus, the blocking of a cortical rhythm when an odor is sniffed in a suppression of activity (Adrian).

The reticular system is adjacent to vegetative centers. Sensory stimuli that would not evoke autonomic symptoms when the subject is awake and expectant will do so when he is asleep (Jung). Both frequency and phase of cortical potential, as shown by the toposcope, vary with the emotional state of the subject. A person held in suspense and subjected to a flickering light produces a toposcopic display similar to that of epileptic patients except that it does not persist (Walter).

The assumption that a center of consciousness has some neuronal substrate implies some location. This should be where the heterogeneous components of present and past experience can form a "whole." The numerous neurons with short axons massed in the small space of the reticular system are uniquely fitted for such a role. Each neuron would lie in the electric field of its active neighbors. The number of units of which one is aware at any one time is limited. It is the sequence of these instants of awareness that contributes to the conscious state. This sequence could be a circulation of impulses within a network of recurrent neurons in such a way that each reverberation activated more synapses than the one before. The mechanism would not be based solely on an all-or-none law of neuronal action. Neurons with such short axons may not develop a true action potential but exert their influence by the current flow between dissimilar parts of the same neuron (somatodendritic potentials). The characteristics of this current flow are critical for the establishment of excitation on the one hand and inhibition on the other. Thus, consciousness is viewed as an integration of perception having both temporal and spatial qualities (Fessard).

Search for Antiepileptic Medicines

Fortunately for the patient, he has not been forced to await complete understanding of the causes of epilepsy. The bromides in 1857, phenobarbital in 1912, and Mebaral in 1932 were employed on an assumption that a sedative was necessary to control seizures. Putnam and Merritt, in 1937, introduced systematic screening of promising antiepileptic substances by testing their ability to protect cats against electrically induced convulsions. The result of their examination of several hundred compounds was the discovery of Dilantin, the first and still the most useful of the nonsedative anticonvulsant drugs. Since that time, many modifications of these animal-screening tests have been developed. These include, in addition to electric shock, injection of Metrazol, hydration, high oxygen pressures and sound stimulus given to mice and rats genetically conditioned. Currently, pharmacologists seem to agree that substances that protect primarily against electric-shock-induced convulsions may be expected to behave clinically much

as Dilantin does, whereas substances that show up well against Metrazol-induced seizures can be expected, like Tridione, to protect against petit-mal seizures. Everett and Toman, in 1951, proposed a modification of the electric-shock type of convulsion that they believed could be used to identify medicines effective against psychomotor seizures in patients. Screening of compounds chemically related to phenobarbital has given most of the newer clinically useful anticonvulsant drugs, Mesantoin, Tridione, Paradione, Phenurone, Milontin and Mysoline. That the animal-screening technic can miss certain drugs that have antiepileptic activity is suggested by failure of Diamox, a useful anti-petit-mal drug, to protect mice against Metrazol-induced convulsions.[23]

Powerful agents fit to join the company of phenobarbital, Dilantin and Tridione may be discovered by other approaches designed to change the metabolic substrate for seizures or even to modify the basic neurochemical lesion of epilepsy. That the phenobarbital-like chemicals are not the solitary hope for epilepsy is suggested by reports of clinical benefit from various substances such as the bromides, sulfonamides,[24] quinacrine,[24] chlortetracycline, Doca (desoxycorticosterone)[23] and glutamine.[22]

Treatment

General Principles

Complete suppression of all epileptic manifestations with minimal impairment of efficiency, the primary objective of therapy, is today best achieved by skillful use of antiepileptic drugs. Those who continue to recommend the ketogenic diet for the treatment of very young patients prescribe it less frequently than in the past, when the bromides and phenobarbital were the only pharmacologic alternatives.

A gratifying unanimity of opinion among clinicians exists on the following principles of treatment:

Tolerance and need for medication vary so greatly from patient to patient that both drug and dosage must be individualized.

Potentialities of full doses of the least toxic medicine are explored first.

Dosage is progressively increased until either seizure control is complete or evidence of overdosage appears.

If well tolerated and completely effective the same prescription is administered for several years until withdrawal is deemed possible.

If the therapeutic trial is unsuccessful the drug is withdrawn.

A partially effective drug is retained, and a similar therapeutic trial is initiated using the next safest medicine as a supplement.

When a drug used singly fails, seizure control is often achieved by a combination of drugs in full dosage.

Sudden withdrawal of effective medication, especially Dilantin or phenobarbital, is dangerous because a plethora of seizures may follow.

Prescribed in suitable doses, none of the antiepileptic drugs cause mental deterioration, although with certain medicines a constant vigil must be maintained for evidence of toxicity.

The early use of effective measures to control a prolonged convulsion or status epilepticus is indicated to avoid the risk of irreversible cerebral changes or even death.

Surgical removal of an epileptogenic focus may be curative in a limited group of patients when medical control fails.

Antiepileptic Drugs

Recent summaries of treatment, although they fully acknowledged the long-established effectiveness of Dilantin and phenobarbital and its homologue, Mebaral, singly or in combination, vary in their enthusiasm for the bromides. Livingston[5] finds them especially useful in children whose convulsions are secondary to brain damage. Others mention their potential value for patients whose convulsive attacks cannot be controlled by other forms of therapy.

Mesantoin (3-methyl-5, 5-phenylethylhydantoin), a homologue of Dilantin, is helpful against convulsive and psychomotor seizures. The dosage, averaging 1 or 2 0.1-gm. tablets a day for a child and up to 6 or 8 0.1-gm. tablets for adults, is usually limited by the sedative effect. Mesantoin is sometimes effective for patients who do not respond to Dilantin or who have severe hyperplasia of the gums. However, it holds the threat of thrombocytopenia or neutropenia or even aplastic anemia in occasional cases, and because of the necessity for monthly blood counts, it is more troublesome to use than Dilantin. A rash, fever or lymphadenopathy developing in the first eight to twelve days requires withdrawal of the drug.

Mysoline (5-phenyl-5-ethyl hexahydrapyramidine-4: 6-dione, 250-mg. tablets) was found to be effective against convulsive and psychomotor seizures by Hanley and Stuart and by Smith and Forster.[25] Livingston reports it to be "exceedingly" effective in controlling convulsions but ineffectual against psychomotor and petit-mal seizures. Because dizziness and sedative effects initially may be troublesome, a portion of a tablet, 50 to 100 mg., is given once a day for several days, with increase in dosage to match acquisition of tolerance. This produces a smoother induction of therapy. No liver, bone-marrow or kidney toxicity has been reported, although a skin rash has been observed in a small group of sensitive patients.[7] Size of dosage is usually limited by the sedative effect. Average daily prescription for young children is 125 mg. three times a day, and that for adults up to 500 mg. three or four times a day.

Hibicon (N-benzyl-β-chloropropionamide, 250-mg. and 500-mg. tablets) is said to be an effective and nontoxic anticonvulsant by several authors. The dos-

age used is approximately 2 gm. a day for children and 6 to 8 gm. a day for adults. Other authors agree that Hibicon is nontoxic but consider its anticonvulsant efficiency low.

Phenurone (phenacetylurea, 0.5-gm. tablets) has been recommended not only as an anticonvulsant, but also as an effective agent against psychomotor and petit-mal seizures. Although it rarely produces drowsiness or other handicapping side effects at therapeutically effective doses and although it is usually nontoxic, Phenurone is not the drug of choice because, in rare cases, it causes toxic reactions of the liver or bone marrow and because it tends to aggravate pre-existent personality disorders in susceptible patients. Liver toxicity is rare — 1 in 250 in one series — and has not been reported in children, although, of course, the number of children given Phenurone is relatively small. Tests that reliably disclose liver injury at an early stage are lacking, and alteration in the thymol turbidity and cephalin cholesterol flocculation is unreliable. Therefore, if clinical symptoms of anorexia or malaise occur, Phenurone should be withdrawn. When these symptoms subside, if liver-function studies are then normal, Phenurone can be reintroduced cautiously. The family should be warned to observe the patient for exaggeration of pre-existent personality disorders, and, of course, routine blood examinations for evidence of bone-marrow depression should be carried out at monthly intervals. Like other anticonvulsant drugs, Phenurone occasionally produces an erythematous skin rash in allergic persons.

Tridione (3,5,5,-trimethyloxazolidine 2-4 dione, 0.3-gm. and 0.15-gm. capsules, 0.15-gm. dulcets and solution, 0.15 gm. per 4 cc.) was the first drug to exhibit specific anti-petit-mal activity and is still the standard against which other anti-petit-mal medicines are measured. Dosage, which averages 0.6 to 0.9 gm. daily for a child and 1.2 gm. for an adult, is usually limited by the appearance of excessive sedation. Reduction of the neutrophils or platelets in the peripheral blood requires monthly blood examinations for its early detection. Depression has been reported in 13 per cent of the patients taking Tridione. Barnett has studied Tridione-precipitated nephrotic syndrome in a well documented case. Patients taking Tridione sometimes complain of hemeralopia, but this bizarre symptom is not related either to other side effects or to excessive dosage and is seldom so troublesome as to cause withdrawal.

Paradione (3-5-dimethyl-5-ethyloxazolidine-2-4 dione, 0.3-gm. pills, concentrated solution, 300 mg. per cubic centimeter), a homologue of Tridione, is similar in its effects and dosage. Depression of the blood has been less commonly reported, and the drug is sometimes effective when Tridione fails.

Milontin (N-methyl-A-phenyl succinimide 0.5-gm. capsules) is found by Zimmerman and Smith and Forster[25] to be helpful against petit-mal seizures, although Livingston has not been able to confirm these findings. In almost 300 patients we have found Milontin definitely potent against petit-mal attacks. Although it is not as regularly helpful as the diones, we prefer it because of its freedom from toxic effects on the blood. Millichap's[26] discovery of evidence of frequent renal toxicity from Milontin has not been confirmed by other reporters.

Diamox (250-mg. tablets), originally chosen on theoretical grounds because of its potency as an inhibitor of carbonic anhydrase and, therefore, a dehydrating and acidifying agent, has been found by us and also by Merlis[27] in an independent investigation to be an effective suppressor of petit-mal attacks. In our experience[24] patients whose electrograms respond excessively to overbreathing are most likely to benefit. There seems to be no advantage in giving doses larger than 3 250-mg. tablets a day, and no toxic side effects have been observed.

Atabrine (quinacrine, 0.1-gm. tablets), in dosages ranging from 0.1 to 0.4 gm. a day, was described as useful against petit-mal attacks by Arellano.[28] Except for the cosmetic handicap of yellow staining of the skin and occasionally some loss of appetite, the substance is free from toxicity. In a group of patients suffering from petit-mal seizures, either alone or in combination with convulsions, quinacrine was found to be beneficial in approximately 12 per cent.[24] Most of the cases in this series were resistant to other anti-petit-mal treatment. A small proportion of patients experienced exaggeration of convulsive attacks while receiving the drug for minor seizures.

ACTH and cortisone have been reported to be convulsant in their action, although Livingston and Kline observed temporary improvement in a small group of children.

Desoxycorticosterone acetate (Doca) has been the subject of several favorable reports regarding its effectiveness in protecting animals against electroshock-induced convulsions and as an anticonvulsant in epileptic patients.

Glutamine, an ammonium salt of glutamic acid, is reported to have produced improved seizure control in several patients. Tower[22] described not only clinical but electroencephalographic improvement in these patients.

A number of homologues of Dilantin, Tridione and phenobarbital as well as several completely new treatments are currently undergoing clinical evaluation in this country and abroad so that it is entirely possible that within the foreseeable future, all summaries of medical therapy of epilepsy will need to be expanded.

Surgery

Hemispherectomy,[4] more accurately termed hemicorticectomy, is the newest development in the surgical treatment of certain cases of epilepsy associated with unilateral brain atrophy. The operation is a

radical removal of all the diseased cortex, including the insula but sparing the basal ganglions, hypothalamus and diencephalon. This radical measure was first proposed by Krynauw in 1950 as a treatment for infantile hemiplegia with epilepsy. A cessation of seizures, paradoxical improvement in spasticity, increased alertness and competence and improved behavior have been reported to follow this procedure. Apparently, the tissue removed not only had served no useful function but also had increased the patient's disabilities.

Complete hemicorticectomy is justifiable in relatively few cases, but electrographically controlled radical excision of nonfunctioning gyri is being more commonly adopted as a treatment for focal seizures uncontrollable by drugs. Because subpial removal of nonfunctioning brain tissue permits adjacent cerebral structures to develop better and in view of the evidence that abnormal areas of the brain exhibiting constant electric dysfunction may exert a damaging influence on the total intellectual and behavioral function of patients, the prophylactic possibilities of gyrectomy deserve additional evaluation.

On the other hand the problem of selecting young patients for surgical treatment is complicated by the consideration that the epileptic character of injured brain tissue may disappear with advancing age.

It seems safe to say that, for the present, conservative methods of treatment should be the first recourse even in patients who have focal attacks based on nonprogressive lesions and that surgery should be considered only in those who have been resistant to more conservative measures.

Social and Psychologic Aspects

If the child or adult with seizures could receive even a fraction of the public understanding, sympathy and support accorded his brothers and sisters with paralytic poliomyelitis many of his most severe handicaps would vanish. Lennox and Markham,[29] in an illuminating article, write as follows:

> Anxiety, uncertainty and fear may accompany any serious disease; however, for the victim of other illnesses there is public sympathy and support and for the epileptic, only public dislike and rejection. The emotions of the epileptic then include shame, depression, bitterness, secrecy and deception. In a vicious circle, consequence becomes cause and anxiety aroused by social mistreatment can precipitate some of the seizures. [They then analyze the causes for public rejection in this way:] The widespread discrimination against the epileptic is the heritage of many centuries during which there was no treatment and the epileptic inmate of the insane asylum or the town idiot was considered representative of all those who had convulsions. [By contrast, although certainly not applicable to all epileptic patients, the following general conclusions refer to most, according to these authors:] Epilepsy is not a mysterious disease and certainly is no disgrace. Simple epilepsy, like diabetes, is a metabolic disorder. It is perhaps an enigma but not a stigma. It does not tend to get worse with time. There are effective medicaments. The mind is rarely affected. A child should continue schooling and the adult should work. Activity is an antagonist of seizures. Marriage and children are not necessarily precluded. Given social acceptance, the great majority of patients can lead normal lives.

The answers to a questionnaire sent to 375 adult office patients seen during 1951 and 1952 included both encouraging and discouraging replies. Of the 173 patients responding, 20 per cent were housewives and students not specifically employed. Eighty per cent of the remaining 140 adults were employed. Seventy per cent said that epilepsy had not prevented their getting a job; however, they did not specify whether prospective employers had been informed of the illness. Approximately 1 in 3 had been discharged from a job because of the epilepsy. A seizure on the job was responsible for 4 out of 5 firings, and in the other the employer had heard of the illness through others.

These authors, in a summary of their experience with 43 epileptic physicians not included in the preceding group, report that only 1 had had to abandon the practice of medicine because of his seizures.

That there has been improvement in public understanding of epilepsy is suggested by a poll[30] of public opinion made in 1949 and repeated in 1954. The earlier survey revealed that 57 per cent of the persons interviewed would not object to having epileptic patients in school with their children, 59 per cent did not think epilepsy a form of insanity and 45 per cent thought that epileptic patients should be employed in jobs like other persons. The more recent poll showed an increase of 9 to 15 per cent in the proportion of favorable replies to the same questions. As might have been expected, those who had had more formal education gave a higher percentage of favorable answers in this poll.

That the public is finally willing to support epilepsy research and a campaign for public education is suggested by the formation of a number of lay organizations, including the National Epilepsy League, 130 North Wells Street in Chicago, and the Epilepsy Association of New York, 123 East Fifty-Second Street, New York City, both of which publish news bulletins. The Epilepsy Information Center at 319 Longwood Avenue, Boston, distributes pertinent educational material presented at the level of the layman.

The efforts of lay organizations have borne significant fruit in obtaining governmental support for the National Institute of Neurological Diseases and Blindness, where epilepsy research has recently discovered the therapeutic value of glutamine. The Physician's League Against Epilepsy not only furnishes professional guidance for lay organizations but also holds scientific meetings of its own and publishes the journal, *Epilepsia*, mentioned at the beginning of this report. A particularly important project sponsored by the Physician's League is a research study of all state laws that pertain to epilepsy. This project, under the leadership of Mr. Roscoe Barrow, dean of the University of Cincinnati Law School, should when completed stimulate professional and lay organizations to join forces in modernizing these laws.

Conclusions

Encouraging progress in the field of epilepsy has been made in the cause, diagnosis and treatment. Evidence of an awakening social understanding of and consideration for their plight forecasts better days for epileptic persons.

References

17. Feldberg, W. Role of acetylcholine in central nervous system. *Brit. M. Bull.* **6**:312-320, 1950.
18. Brink, F., Jr. Role of potassium in activity of nerve cells. *Journal-Lancet* **73**:171-173, 1953.
19. Terner, C., Eggleston, L. V., and Krebs, H. A. Role of glutamic acid in transport of potassium in brain and retina. *Biochem. J.* **47**:139-149, 1950.
20. Weil-Malherbe, H. Glutamic acid and its relation to nervous system. In *Metabolism and Function in Nervous Tissue: A symposium held at the London School of Hygiene and Tropical Medicine on 10 November 1951.* Edited by R. T. Williams. 102 pp. London: Cambridge University Press, 1952. Pp. 16-26.
21. Tower, D. B., and Elliott, K. A. C. Experimental production and control of abnormality in acetylcholine metabolism present in epileptogenic cortex. *J. Appl. Physiol.* **5**:375-391, 1953.
22. Tower, D. B. Nature and extent of biochemical lesion in epileptogenic cerebral cortex: approach to its control in vitro and in vivo. Presented before the annual meeting of the American Academy of Neurology, Washington, D. C., May 1, 1954.
23. Toman, J. E. P., and Taylor, J. D. Mechanism of action and metabolism of anticonvulsants. *Epilepsia* **1**:31-48, 1952.
24. Davidson, D. T., and Lombroso, C. Unpublished data.
25. Smith, B., and Forster, F. M. Role of some experimental anticonvulsants, mysoline, milontin and 1461-L. *M. Ann. District of Columbia* **22**:279-282, 1953.
26. Millichap, J. G. Milontin: new drug in treatment of petit mal. *Lancet* **2**:907-910, 1952.
27. Merlis, S. Carbonic anhydrase inhibitor: its use in epilepsy. Presented at a joint meeting of the American Academy of Neurology and the American League Against Epilepsy, Washington, D. C., May 1, 1954.
28. Arellano, Z. A. P. Promising approach to study of epilepsy: seizure activating and inhibiting effects of two groups of new drugs. Presented at the Third International Congress of Electroencephalography, Cambridge, Massachusetts, August 20, 1953.
29. Lennox, W. G., and Markham, C. H. Sociopsychological treatment of epilepsy. *J.A.M.A.* **152**:1690-1694, 1953.
30. Cavenes, W. Survey of public attitudes toward epilepsy. *Epilepsia* **1**:19-26, 1949.

MEDICAL INTELLIGENCE

THE PHYSICIAN AND THE HOSPITAL ACCREDITATION PROGRAM

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THE hospital administrator has been given a burden in the form of added duties to keep his medical staff busy writing records and holding consultations so that the hospital may retain its rating. Many physicians think that all this extra paperwork takes much valuable time that could be used to better advantage. Thus, the administration and the medical staff need to understand one another on this important matter.

Few physicians have any knowledge of hospital organization. They have no interest in the functions and the power of the governing board of the hospital, which approves the appointments to the medical staff, or in the work of the committee on tissue or medical records except, perhaps, to suspect that such activities interfere with their personal freedom to practice as they wish.

A physician who has a practice limited to his office or who also makes house calls, but does not practice in a hospital, can have a record system to suit himself: it can be simple or elaborate, or he may decide to keep no records at all. But as soon as he becomes a member of a medical staff in a hospital he accepts the rules and regulations created by the staff and approved by the governing body of the hospital. If he does not comply with these rules and regulations his privilege of practicing in the hospital may be withdrawn.

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The hospital administrator is a co-ordinator. He sees to it that all departments function properly and acts as a liaison between the medical staff and the administration of the hospital.

If more physicians had an opportunity to become better acquainted with the principles underlying the bylaws and the rules and regulations of hospital staffs to which they have been appointed, they would probably be more co-operative. Some of these principles may be briefly enumerated. In the first place a descriptive outline of the medical organization and a procedure for granting and withdrawing privileges to physicians to work in the hospital are essential. The necessary qualifications for appointment to the staff should be stated, with a definite and specific prohibition against division of fees under any guise whatever. Regular meetings of the medical staff should be provided for, and facilities for accurate and complete clinical records should be available. The clinical records should be written by a physician for all patients treated in the hospital and should be completed at time of discharge. It should also be understood that the physician in charge of the patient is responsible for seeing that all tissue removed at operation is delivered to the pathologist. Provisions for routine examination of all patients on admission and recording of diagnosis before operation should be made. There should be rulings permitting a surgical operation only on consent of the patient or his legal representative and providing that consultations be held on all critically ill and obscure cases. Finally, it should be required that a physician's orders be written and signed by him.

Hospitals are examined from time to time and are rated according to the standards maintained. Records reflect the type and grade of work done — at least the examiner who evaluates the work done in the hospital has to go by the records he has before him. There are many examiners: the local board of health, which is not too demanding, and the state board of health,

which issues the license to run the hospital. Until a few years ago the American College of Surgeons made a comprehensive examination of the hospital. (And which hospital did not want to be approved by the American College of Surgeons?) Now, instead of the American College of Surgeons and the examiners of the American Medical Association, there is the newly formed Joint Commission on Accreditation of Hospitals, which is sponsored by the following organizations: American College of Physicians, American College of Surgeons, American Hospital Association, American Medical Association and Canadian Medical Association.

The examiners of the Joint Commission on Accreditation of Hospitals will be in the Boston area this fall. They will examine several hospitals, all of which are anxious to receive their certificate of approval. This is the time for the records and the tissue committees to ensure that all staff physicians understand and comply with the regulations of the hospital.

Some of the items that the examiners look for in the medical-records department include a complete history, physical examination and provisional diagnosis on every chart; routine laboratory reports; signature of physician on all orders; adequate progress notes; consultation on all questionable cases; preoperative and postoperative diagnosis; performance of operation only when the chart shows the necessity; and reports of operation before the surgeon leaves the hospital.

In the maternity ward the prenatal record comprises a physical examination (including pelvic measurements) and laboratory reports. There should also be a labor record, as well as a report of the physical examination of the newborn infant before it is taken from the delivery room and a final examination when the infant is discharged.

When the patient is discharged the record should be completed.

The examiners are impartial, but they are thorough and efficient. They examine hospitals all over the country and know what is going on. They are aware of the answers to all excuses and of the fact that the record reflects the type of work done by the physician. They expect a good record to be well written and in chronologic order. An incomplete record on the floor will more than offset points gained on completed records in the record room.

In conclusion a statement by one of the examiners* is pertinent:

> The two divisions where deficiencies will most affect the accreditation status of a hospital are medical staff organization and the medical records department, both essential divisions (see *Hospitals* April, 1954). Responsibility for adequately fulfilling the requirements of these divisions rests primarily on a single group — the physicians themselves. Deficiencies noted in these two sections are often the deciding factor in whether or not a hospital is to be accredited. To attain this objective, the full cooperation of the medical staff and each of its members is essential: the medical staff can "make or break" a hospital's opportunity for accreditation.

*Hess, G. R. Inadequacies of hospitals in meeting accreditation requirements. *Hospitals* **28** (No. 5):94-96, 1954.

I trust that this brief consideration of the problems involved will demonstrate that hospitals expect the full co-operation of staff physicians in the campaign for better records.

BY THE LONDON POST

Art of Medicine — Achievement or Security? — Influence of Television

JOHN LISTER, M.D.

LONDON, ENGLAND

FINE words are spoken and high ideals are set as each new academic year begins. Men of eminence address the students of medical schools and define for them the principles of the profession. Many of those who have spoken to students this year have stressed the fact that medicine remains an art even though it has been caught up in the rapidly advancing social and scientific resolutions of the day.

Lord Dawson of Penn once said that medicine was an art based on many sciences. Recalling this in a speech at the Royal Free Hospital, Mr. A. N. Gilkes, high master of St. Paul's School, warned the students that their patients were in need of something that went beyond science. He said that a physician must show sympathy, understanding and friendship and indeed a certain love for mankind. Sir Russell Brain, F.R.C.P., also urged the students at King's College Hospital to cultivate these qualities. He believed that medicine may be regarded as the art of human relations and that the doctor remains a stable point in a changing world. Physicians, being themselves part of society, must be subject to the same social, political, artistic and philosophic influences as other members of society, but in a world of change the best qualities any man could possess would be those of patience and understanding. These were the qualities that would equip the doctor to practice the art of human relations when confronted with such human situations as birth, disease and death.

At the opening ceremony of the Birmingham Faculty of Medicine, Sir Richard Livingstone contrasted the immense successes of science with the much less impressive achievements in the fields of private and public conduct. He recalled that the Greek thinkers had met a similar problem when they were confronted with the impact of a scientific view of life on accepted values. Sir Richard thought that the greatest present need was for a philosophy of life that would provide a clear judgment of what is good and what is bad. He thought that this could be found in the Christian view of the good life as the life of love.

Sir Geoffrey Vickers, V.C., addressed the students of University College Hospital and spoke about the relation between the professional man and the lay-

man he was advising. He said that it must be thought of as a partnership and described the practice of a profession as "the exercise of insight, that human faculty which is of all faculties the most delightful in its exercise and the most blessed in its results."

It is well to have this annual opportunity for moral stocktaking and for defining the principles of the profession, for thoughts such as these will help to ensure that medicine remains an art and that it may carry with it a high sense of vocation.

* * *

Many tests have been devised to help assess an applicant's suitability for medical training, and much has been written about the ideal medical student. The problem of how to find him was widely discussed at the first World Conference on Medical Education in London last year, and it is a subject that comes into prominence at the beginning of each new academic year.

In this country, since the war, there has been a great increase in the numbers of applicants for admission to medical schools, but some of those who select students believe that there has been a decline in the quality of the applicants. In particular a change in the motive behind a young person's choice of medicine as a career has been observed. In some cases a desire for achievement seems to have been replaced by a desire for security. This attitude of mind is perhaps a by-product of the National Health Service, for this appears to offer a guaranteed livelihood. Nevertheless, the Medical Practice Committee has issued a serious warning in its fifth annual report, that the young physician may expect to find it increasingly difficult to obtain employment. The committee believes that the process of approaching saturation in the total number of general practitioners in the National Health Service has been greatly accelerated. The trend toward a more even spread of doctors throughout the country has continued during the last year, and there has been an increase in the number of practitioners in "underdoctored areas." Furthermore, there may now be as many as 100 applicants for a vacancy in a good practice in a popular area.

The Committee regards it as urgent that all aspects of this problem be considered at the highest level. It points out that an assessment of the optimum needs of the medical services in terms of manpower depends not only on the numbers eligible and those for whom places in medical schools could be found but also on the development that rational finances would at any time permit. It also states that the claims of other professions on the available manpower must be borne in mind. It is somewhat paradoxical that, at the same time as saturation is being declared in the National Health Service, the present position of the medical services of the armed forces is described as "little short of desperate" because of lack of medical officers. This shortage of medical personnel is predominantly due to the diminished material and professional attractions of a service career, compared with the opportunities open to the young doctor in the National Health Service. On the other hand, it is becoming increasingly clear that there is not unlimited opportunity in the National Health Service. Indeed, more than 2500 students have just entered the medical schools and the *British Medical Journal* has questioned whether they will all be able to find a satisfactory permanent livelihood at the end of their trek to medical graduation.

* * *

Whatever one's feelings on the merits or shortcomings of television, the fact remains that it is yet another advance with which one must come to terms. Widely differing views on the effects of television have been expressed. At one extreme are those who describe a syndrome of television hysteria, whereby the screen has acquired a tremendous power over millions of people in their own homes. At the other extreme are those who maintain that television has enriched family life and brought to many homes an element of culture that was previously absent; this view was expressed by a group of psychology students in Coventry, who last year carried out a survey into the effects of television on the home. They found that the attraction of television generally lessened after the first year. Topical and current affairs, plays, opera and ballet were frequently mentioned as subjects of new interest to viewers, and though television had reduced the average time spent outside the home on pleasure, there was no evidence that the people of Coventry had allowed themselves to become slaves to the screen.

The greatest criticism of television has been that of its effect on the young. For this reason the Nuffield Foundation has planned a two-year study on the impact of television on children and young people. Scientists, educationists, statisticians and psychologists will comprise the team, and the main emphasis will be on the mental, moral and spiritual influences of television. The B.B.C. has promised the project its full support and states that the corporation itself is carrying out an investigation into the effects of television on adults.

The results of these surveys will be awaited with interest, and it is hoped that the findings will be particularly noted by those who plan television programs.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40471

PRESENTATION OF CASE

A sixty-five-year-old housewife was admitted to the hospital because of vaginal spotting.

Two months previously she noted a 30-pound weight gain (from her usual weight of 226 to 256 pounds). She also observed exertional and nocturnal dyspnea, and peripheral edema. A physician put her on a regimen of a low-calorie, low-salt diet, digitalis and ammonium chloride; however, there was very little improvement. A week before admission she first noted vaginal spotting, which persisted.

She had always been obese but had enjoyed good health. Except for a tonsillectomy at the age of thirteen, she had had no previous past illnesses or hospitalizations. She had had 5 pregnancies, with 4 normal deliveries and 1 miscarriage. Menses had started at the age of thirteen and continued normally until the menopause at the age of forty-two. She had had no vaginal bleeding since the menopause until a week before admission. She denied any urinary or gastrointestinal symptoms. There was no history of alcoholism. She had worked in a tannery for a number of years about twenty-five years before admission.

Physical examination revealed a very obese woman with a plethoric face who had moderate dyspnea while lying flat in bed. The neck veins were not distended. There was + + + pitting edema to the knees. The right side of the chest was clear to percussion and auscultation. The entire left side of the chest, from the spine of the scapula down, was dull to percussion, and breath sounds were diminished; a few inconstant inspiratory rales were heard. The left border of the heart could not be defined because of the obesity. The point of maximal impulse was in the fourth intercostal space inside the anterior axillary line. The heart sounds were of good quality; there were no murmurs. Abdominal, pelvic and rectal examinations were negative.

The temperature was 98.6°F., the pulse 104, and the respirations 16. The blood pressure was 145 systolic, 80 diastolic.

Urinalysis was negative. Examination of the blood showed a hemoglobin of 12.4 gm. per 100 cc. and a white-cell count of 5400. The sodium, chloride, potassium and sugar levels were all within normal limits. The prothrombin time was 16 seconds (normal, 13 seconds), or 50 per cent of normal. The total protein was 7.3 gm., the albumin 2.7 gm., the globulin 4.6 gm., the alkaline phosphatase 1.6 units, the cholesterol 120 mg., the cholesterol esters 60 mg., the nonprotein nitrogen 24 mg., and the total bilirubin 1.9 mg. per 100 cc. Cephalin flocculation was + + + + in forty-eight hours. Thymol turbidity was 7.5 units, and thymol flocculation + + +. Bromsulfalein retention was 73 per cent. The blood carotenoids were 1.1 units per cubic centimeter. The vitamin A blood level was 0.4 units per cubic centimeter. A stool was guaiac negative. An electrocardiogram revealed a normal sinus rhythm and a pattern suggestive of digitalis effect. An x-ray film of the chest showed a large amount of fluid in the left pleural space. The mediastinum was shifted slightly to the right. The left apex and right lung were clear. A plain film of the abdomen was unsatisfactory because of obesity. A second x-ray film of the chest after 940 cc. of serosanguineous fluid had been removed from the left side of the chest demonstrated no definite tumor mass, though a hazy shadow just above a residual fluid level was noted. A cell block of the chest fluid was reported as "negative for tumor cells," and a smear on the same fluid was reported as "doubtful." A vaginal smear showed 92 per cent of the cells cornified and was reported "positive for tumor cells." An endometrial smear was reported as "doubtful." FSH (follicle-stimulating hormone) determinations on the urine were negative for 96 and 192 mouse units per twenty-four hours (normal, 96-600 mouse units). A cervical biopsy showed chronic cervicitis; a biopsy of the endometrium was insufficient for diagnosis.

The patient was fairly well until the evening of the sixteenth hospital day, when she suddenly became confused and semistuporous and cried out that she was falling through space and dying. She had received 500 cc. of fat intravenously that morning; otherwise no unusual events had transpired during the day. The sodium was 109 milliequiv., the potassium 3.6 milliequiv., the chloride 77 milliequiv., and the carbon dioxide 26 milliequiv. per liter. The blood ammonium level was 253 microgm. per 100 cc., falling to 159 microgm. after administration of sodium glutamate. This level was maintained throughout the following day. She was treated with 6 per cent saline and sugar glutamate mixture, and on the next day the blood ammonium level had fallen to 74 microgm. per 100 cc.; the sodium was 130 milliequiv., the chloride 83 milliequiv., and the potassium 5.3 milliequiv. per liter. She was somewhat improved. The blood pressure had fallen to 70 systolic, 50 diastolic,

and she was oliguric. The nonprotein nitrogen was 123 mg. per 100 cc. She died on the twenty-second hospital day.

Differential Diagnosis

Dr. Alfred Kranes*: This case contains features, of which some are clear and others puzzling. Starting with the obvious, one would have to say that this woman was suffering from severe liver disease, although it was not apparent on clinical grounds. There was no previous history of jaundice, and the physical examination revealed none of the usual accompaniments of liver disease. There was no hepatic enlargement or ascites, although a large liver may have been present in this obese woman's abdomen without its being palpable. She had no spider angiomas and no enlargement of the spleen. Even though I am reluctant to make a diagnosis solely on laboratory data, the imposing array of abnormal liver-function tests — low serum albumin, slight icterus, low cholesterol esters, positive flocculation tests and increased bromsulfalein retention — seems to make a diagnosis of severe liver disease practically mandatory. Furthermore, she died in what appears to have been hepatic failure. What took place on the sixteenth hospital day to produce this sudden change in the picture is not clear from the history. The usual precipitating causes of hepatic failure do not seem to have been present. She had no severe hemorrhage or acute infection. One wonders what she had in the way of therapy that could possibly have been responsible. Was she given any diuretics, a high-protein diet or ammonium chloride?

Dr. Nathaniel J. Ehrenkranz: This patient was unable to take very much by mouth so that there was no high-protein diet. Although ammonium chloride may have been given very early, it was not given up to a few days before death, and I do not think it contributed to the end result. I am not sure when the endometrial biopsy was done.

Dr. Benjamin Castleman: The endometrial biopsy was done a week before she died.

Dr. Kranes: The anorexia interests me since nothing is said about any gastrointestinal symptoms in the protocol.

Dr. Ehrenkranz: I think she was nauseated a great deal.

Dr. Kranes: I am puzzled by the striking drop in the serum sodium and chloride levels. She only had one thoracentesis?

Dr. Ehrenkranz: She had more than one; she had more than one abdominal paracentesis too.

Dr. Kranes: Nothing was said about any ascites!

Dr. Castleman: An abdominal tap was done two weeks before she died. One hundred and ninety-five cubic centimeters of clear fluid, which showed no evidence of malignant cells, was removed.

Dr. Kranes: I was trying to find out whether enough fluid was removed to have been responsible for the marked salt loss. Apparently, not enough was removed to produce such a result.

The ascites is additional evidence that we are dealing with severe liver disease.

It seems to be implied that the fat given intravenously was a possible cause of the hepatic failure or hyponatremia. Dr. W. R. Waddell tells me that, as far as he knows, no deleterious effects on serum electrolytes are known to occur after fat has been given intravenously, and I doubt very much if this could have been responsible. I was at first puzzled about why it was given to her at all, since nothing was said about her having been a nutritional problem. She was very obese.

Dr. Ehrenkranz: She was a nutritional problem.

Dr. Kranes: I have no idea about the sort of liver disease the patient had. There are no clues to its nature — no history of alcoholism. Perhaps she was an alcoholic and we do not have the history. She had never been jaundiced. I can go no farther than to say she had severe liver disease and that the commonest type of liver disease producing this picture is cirrhosis. It might have been helpful to have given her a swallow of barium to see whether there was any evidence of varices.

Will liver disease explain all the findings in this patient? I do not think so, although it might. The two features hard to explain are the vaginal spotting and the bloody effusion in the left thorax. The vaginal bleeding may have been caused by severe hepatic insufficiency, which may result in other hemorrhagic phenomena; however, one would not expect the vagina to be the only site of bleeding, without nosebleed, bleeding from the gums or ecchymoses. Furthermore, the prothrombin time was not very abnormal. When patients with severe liver disease have pleural effusions, they are more likely to be present on the right side than the left. Moreover, the effusion is not likely to be bloody. Nothing was said in the record about the specific gravity of the fluid.

Dr. Castleman: The specific gravity is not recorded.

Dr. Kranes: Did this woman, in addition to severe liver disease, have cancer? The bloody pleural effusion, the vaginal bleeding and the cytologic reports make one wonder. The cytologic reports indicate a high probability (about 95 per cent) that this patient had cancer of the genital tract. The number of falsely positive vaginal smears in this hospital is now approximately 5 per cent. Is that a fair statement, Dr. Ulfelder?

Dr. Howard Ulfelder: Yes.

Dr. Kranes: So that the odds are very strongly in favor of genital carcinoma. It would be folly to ignore such a finding unless there were very compelling reasons for doing so. I am therefore going to assume that she had a carcinoma of the vagina, cervix, endometrium, tube or ovary. Since the surgeons had

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a good look at the vagina and obtained a negative cervical biopsy, the most likely site for carcinoma is the endometrium. There is a remote possibility that it was a fallopian tube although that is a rare site for carcinoma.

There are two disturbing findings that I do not know how to interpret. The first is that this postmenopausal woman had no elevation of FSH; the second is that she had a cornified vaginal epithelium. Those two findings indicate an estrogen effect. Either this patient took some estrogen, or else she was producing estrogen. Male patients with cirrhosis often have evidence of estrogen effect in that they may have gynecomastia, atrophic testes, loss of chest hair and spider angiomas. These have been attributed to the inability of the sick liver to conjugate estrogen, which may be produced perhaps in the adrenal gland. It occurred to me that the estrogen effect here might have been on a similar basis. I do not know how valid this assumption is since I have never seen any work done on it. Do you know whether or not she had been taking estrogen?

DR. EHRENKRANZ: She had not.

DR. KRANES: If we assume that she had not, and if the liver disease was not responsible for these findings, one must consider the possibility of an ovarian tumor that was secreting estrogen and may have been responsible for some of the vaginal bleeding. It seems to be an unlikely explanation because such ovarian tumors — granulosa-cell and theca-cell tumors — are extremely rare and would not satisfactorily explain a vaginal smear positive for tumor cells. It is conceivable that malignant cells from an ovary might pass through a tube and be found in the vaginal smear. Although such occurrences may have been reported they are decidedly unusual. Furthermore, such ovarian tumors are not highly malignant and would not metastasize without a palpable pelvic mass. I should like to see the chest films.

DR. JOHN F. GIBBONS: The effusion in the left pleural cavity is obvious. The flat fluid level is due to the fact that a little air must have been introduced at the time of the thoracentesis. I believe that the shadow above the fluid can be explained on the basis of thickening in one of the fissures and a little atelectasis. At least I should not dare say that there is a mass in the lung above the fluid, and I do not think there is. The films of the abdomen do not help too much except that there is a haze over the abdomen. I cannot tell whether the haze is due to the great obesity or to fluid, but we know that the patient did have fluid. I am afraid I cannot outline the liver and spleen adequately to tell you much about them.

DR. KRANES: May I ask about the serosanguineous effusion? How bloody was the fluid?

DR. CASTLEMAN: The report reads as follows:

> Nine hundred and forty cubic centimeters was removed. The procedure was stopped because of slight pain in the shoulder and because no more fluid could be obtained; 240 cc. of air was injected. The ratio of red to white cells was about 10:1 — 12,000 red cells and 1300 white cells.

DR. KRANES: I am assuming that the fluid in the left side of the chest was not the result of liver disease. Since a cancer in the pelvis, probably in the endometrium, seems likely I shall assume that the fluid was due to metastatic disease. It may have been due to an infarct, but there was no history that leads me to suspect it in any way.

If the patient did have an endometrial cancer, did it have any relation to the severe liver disease? Cancer can produce symptoms of hepatic insufficiency in one of two ways. By far the commonest is by extensive metastases. If so the liver should have been easily palpable, — a huge liver, — and there should have been more discomfort. Furthermore, the alkaline phosphatase should have been markedly elevated. Another way in which cancer can produce liver insufficiency is by obstruction of the hepatic veins and the production of a Chiari syndrome. This is unusual, but in view of the fact that I think there was some metastatic disease in the chest I cannot help thinking of the possibility. Usually, in a person past middle age, one is on somewhat safer ground if one does not try to tie all the loose ends together but makes several diagnoses. I shall therefore suggest that the patient had cirrhosis of the liver, cause unknown; that she had a carcinoma, probably of the endometrium, with metastases to the chest; and I wonder whether the hepatic veins were obstructed.

DR. WILLIAM H. BAKER: There seems to be good evidence that there was some overproduction of estrogens in this patient as shown by the low FSH, cornification of the vaginal epithelium and uterine bleeding. I should think that an ovarian carcinoma, which is estrogen producing and which does predispose to cancer of the endometrium, or an estrogen-producing tumor of the adrenal gland might be possibilities. Dr. Earle Engle, at Columbia University, believes that the estrogen-producing tumors of the ovaries are not all granulosa-cell tumors; he believes that they are thecomas and that if granulosa-cell tumors of the ovaries produce estrogen they are mixed granulosa-cell and theca-cell tumors. It was formerly believed that only granulosa-cell tumors produced estrogen. I should think that an ovarian tumor that produced estrogen is a distinct possibility.

DR. ULFELDER: It is worth pointing out that there are a number of cases of positive vaginal smears in women who had cancers of pelvic peritoneal surfaces without any tumor involving a genital organ so that such smears do not necessarily localize cancers to the pelvis. The cancer might be in the chest with metastases downward with positive peritoneal effusion and a positive vaginal smear from that.

DR. DANIEL S. ELLIS: I think that if this patient had a cancer, it was cancer of the liver superimposed on cirrhosis.

DR. CASTLEMAN: Are there any other suggestions?

DR. JACOB LERMAN: When this case was discussed at a medical conference, the question of hyperestrinism was raised because of the vaginal smear and the low FSH in the urine. On the basis of some preliminary studies, which Dr. Goldsmith and I did, I suggested that cirrhosis could produce hyperestrinism and therefore the whole picture could be explained on the basis of hyperestrinism.

DR. KRANES: What whole picture?

DR. LERMAN: The vaginal bleeding.

DR. KRANES: You do not mean the entire picture?

DR. LERMAN: No; the cirrhosis was causing the hyperestrinism.

DR. LEWIS L. ENGEL: Studies of steroid excretion in this case revealed a low titer of 17-ketosteroids (3 mg. per day) and a urinary level of fluorogenic phenols that was consistent with the postmenopausal state. The estrogen effect observed was probably not ascribable to hypersecretion, but may be explained by impaired ability of the liver to conjugate and inactivate the small amounts of circulating estrogen present in a postmenopausal woman.

DR. CASTLEMAN: Dr. McArthur, have you any comment?

DR. JANET W. MCARTHUR: For the benefit of the gynecology postgraduate students* who are in attendance today we might review briefly some current views concerning the role of the liver in estrogen metabolism. Although there are many gaps in our knowledge it appears that the liver is involved in the fate of the estrogens in two ways: by excreting the estrogens into the bile, and by metabolizing estrogenic compounds.

After secretion into the duodenum the estrogens are, to a large extent, reabsorbed and returned to the liver in the portal circulation. During successive passages through the liver the estrogenic compounds are subjected to a variety of metabolic alterations, the majority of which are in the direction of lesser activity (although recent evidence suggests that estrogen activation, the formation of compounds with greater estrogenic activity, may occur to some extent). The inactivation processes are thought to be of three general types: transformation to estrogen conjugates, transformation to estrogen isomers and transformation to inactive products at present of undetermined nature. The resultant of all these processes is complete inactivation.

An experimental study that may have some relevance to the case under discussion is that of Zondek and Black.† Starting from the fact that in normal persons only 0.5 to 4.5 per cent of a test dose of estrogen is recoverable in the urine, these investigators performed serial tests of estrone clearance in patients with acute and chronic liver disease. They found that in advanced cirrhosis a greater proportion of the test dose of estrogen appeared in the urine unchanged, confirming the fact that the rate of metabolic handling of estrone is impaired. In acute hepatitis, the capacity to inactivate estrogen proved to be a very resistant function, outlasting hepatic capacity to synthesize urea in a few cases of very severe damage. Loss of ability to change the administered estrone into inactive compounds was found to imply a poor prognosis both in acute and in chronic hepatitis.

In the case under discussion the low nonmenopausal levels of FSH implied that physiologically effective amounts of estrogen were circulating. It appears that the vaginal bleeding that occurred in consequence may therefore have been an indication of severe liver damage and impending death.

*Harvard Medical School Courses for Graduates.

†Zondek, B., and Black, R. Estrone clearance test in infectious hepatitis. *J. Clin. Endocrinol.* 7:515-529, 1947.

CLINICAL DIAGNOSES

Portal cirrhosis.
?Carcinoma of endometrium.
?Granulosa-cell tumor of ovary.

DR. ALFRED KRANES'S DIAGNOSES

Cirrhosis of liver, type undetermined.
Carcinoma of endometrium.

ANATOMICAL DIAGNOSES

Portal cirrhosis, Laënnec type.
Hyperplasia of endometrium, severe.
(Hyperestrinism.)
Ascites.
Hydrothorax, left.
Pleuritis, chronic, adhesive, left.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At autopsy we found a very cirrhotic liver; it was of about normal weight, indicating that it had probably been much larger and had shrunk to this size. The nodules were fairly uniform, and on microscopical examination I thought it was a portal cirrhosis of the Laënnec rather than the postnecrotic type. There was a fair amount of fat, but we could not find any alcoholic hyalin. There was ascites, which was not hemorrhagic, and a little pleural effusion on the left side that was not hemorrhagic at the time of autopsy. There was no evidence of any tumor or inflammatory reaction in the ascitic fluid or in the pleural space. The right pleural cavity was completely obliterated by adhesions, which probably prevented fluid from accumulating there. The lungs were not remarkable. I do not know why hemorrhagic fluid was obtained on both taps. The red cells were crenated so that I gather it must really have been hemorrhage. It may have had something to do with the poor liver function.

DR. KRANES: That is a very unusual type of fluid in liver disease.

DR. CASTLEMAN: Yes; Dr. Frederic C. Goetz confirms the fact that it was serosanguineous.

The uterus had a great deal of endometrium, — I am surprised that the biopsy had been insufficient, —

which showed a very severe hyperplasia, definitely abnormal for a woman beyond the menopause. It was the classic picture of hyperplasia: markedly dilated and thickened endometrial glands, but no evidence of carcinoma. We made almost serial sections of the endometrium so I think we can be fairly certain that there was no cancer. I suppose it was the hyperplastic cells that were responsible for the positive vaginal smear. Is it not true, Dr. Ulfelder, that the 95 per cent accuracy actually applies to the cervical cancers, and that in the endometrial cancers the average is not so high?

DR. ULFELDER: It all depends on how one calculates the statistics. What Dr. Kranes was saying was that a smear called positive in the absence of cancer is very rare. It is true that of the cancers that we see perhaps 90 to 92 per cent are diagnosed correctly in the cervix and perhaps 80 to 85 per cent in the endometrium. But if there is a positive smear, the chances of its being false positive are less than 5 per cent. I think hyperplasia in the endometrium would introduce an additional factor because there are many abnormal cells in this type of endometrium and the smear could look suspicious.

DR. CASTLEMAN: The ovaries showed focal stromal hyperplasia, a finding that one usually does not expect in a woman beyond the menopause. Stromal hyperplasia occurs, however, frequently enough to make it hazardous to suggest that the whole hyperestrinism effect in this case originated in the ovaries.

DR. FARAHE MALOOF: What about the pituitary gland?

DR. CASTLEMAN: We were unable to examine the head.

DR. WILLIAM H. BAKER: Were the adrenal glands normal?

DR. CASTLEMAN: Yes.

DR. FRANCIS M. INGERSOLL: I thought the patient had a functioning ovarian tumor.

DR. CASTLEMAN: One of the ovaries had a follicular cyst about 2 cm. in diameter. It would have been interesting to have had it assayed for estrogens.

CASE 40472

PRESENTATION OF CASE

First admission. An eight-year-old girl was admitted to the hospital because of intermittent abdominal pain.

Ten days previously steady, moderately severe periumbilical pain, which lasted for two days, developed. During the ensuing week the pain returned sporadically but always remitted spontaneously. On the day before admission, the pain reappeared and was severe enough to disturb sleep during the night. No nausea, vomiting or diarrhea accompanied the pain, and a normal bowel movement was noted on the evening before admission.

Physical examination revealed a well developed, well nourished girl in no distress. Positive findings were limited to the abdomen, which, although soft, showed very active peristalsis and tenderness in the midlower portion but no spasm. Rectal examination disclosed right-sided tenderness. No pelvic examination was done.

The temperature was 100°F., the pulse 96, and the respirations 22. The blood pressure was 90 systolic, 50 diastolic.

A single specimen of urine had a specific gravity of 1.010 and gave a + test for albumin; the sediment contained 75 red cells, occasional white cells and 5 epithelial cells per high-power field. The hemoglobin was 13.6 gm. per 100 cc., and the white-cell count 16,000, with 72 per cent neutrophils. A stool was brown and guaiac negative.

On the next day the patient felt well, and the white-cell count was 8900, with 56 per cent neutrophils. On the third hospital day a barium-enema examination was negative, and she was discharged without therapy.

Second admission (three years and nine months later). She was readmitted to the hospital because of attacks of left-flank pain, which had occurred approximately once a week for two years. On the morning of admission, sharp colicky left-flank pain, which radiated inferiorly (but not into the groin), developed. This subsided but recurred early in the evening; at this time, during micturition, a most severe bout of pain, which caused the patient to writhe and vomit, developed. The mother stated that the urine had a foul odor, and that the patient had noted urinary urgency and frequency, without dysuria.

Physical examination showed a well developed, moderately obese girl in acute distress. The abdomen was soft and slightly distended, with hypoactive peristalsis but without tenderness or spasm. There was no costovertebral-angle tenderness. The liver edge was felt 2 fingerbreadths below the right costal margin, but no other organs or masses were found. The skin, head, chest, extremities and nervous system were normal. Pelvic and rectal examinations were not done. The vital signs were normal.

The urinary sediment contained a few white cells but no crystals. Examination of the blood revealed a hemoglobin of 13.6 gm. per 100 cc. and a white-cell count of 11,200, with 71 per cent neutrophils. The uric acid was 4.2 mg., the calcium 10.5 mg., the phosphorus 4.6 mg., and the alkaline phosphatase 16.4 units per 100 cc.

On the day after admission cystoscopy and bilateral retrograde pyelography were done. On the left the urinary tract was normal; on the right, the calyxes were questionably rounded and blunted. The findings were thought to be consistent with chronic pyelonephritis on the right side though this diagnosis was questioned. A culture of the urine was negative. Indigo carmine was promptly excreted by both kidneys. A gastrointestinal series demonstrated upward dis-

placement of small-bowel loops (Fig. 1).

Therapy consisted of Demerol and Gantrisin. The pain shortly subsided, and the patient was discharged on the fourth hospital day.

Third admission (seven weeks later). Since discharge, she had had intermittent, transient bouts of left-flank pain with accompanying pain in the left middle portion and left lower quadrant of the abdomen. It was noted that an acute episode was accompanied by writhing in bed, crying out, a nauseous feeling and occasional vomiting or retching. The episodes usually ended abruptly, with lingering mild afterpain. During the attack micturition accentuated the pain. On the day of admission, the patient had a typical acute episode, during which the abdomen was generally soft, with great tenderness in the left flank and left lower portion of the abdomen anteriorly. Rectal examination produced loud outcries of pain and was vigorously resisted. An enema two days before admission gave good results, with brown feces.

On physical examination the patient was in obvious distress and was lying in the right lateral decubitus

FIGURE 1. *Roentgenogram from Gastrointestinal Series. The upward displacement of barium-filled small-bowel loops is indicated by arrows.*

position with her legs drawn up. The abdomen was soft and moderately tympanitic, with hypoactive peristalsis and considerable tenderness in the left lower quadrant and suprapubic area. No rebound tenderness was found. A tumor in the area of tenderness was questionably palpable. Rectal and pelvic examinations were omitted.

The temperature was 98.6°F., the pulse 88, and the respirations 20. The blood pressure was 95 systolic, 65 diastolic.

Urinalysis revealed a specific gravity of 1.024 and 3 to 5 white cells per high-power field in the sediment. The hemoglobin was 13.8 gm. per 100 cc., and the white-cell count 14,600, with 84 per cent neutrophils.

On the following morning the patient had no pain or soreness. Pelvic inspection revealed a cloudy discharge from an irritated, virginal introitus. On rectal examination, no abdominal tenderness or mass could be palpated. A small, developing cervix was delineated. A white-cell count was 12,700, with 68 per cent neutrophils. A glove stool specimen was strongly guaiac positive.

Just after midnight on the next day, the temperature rose to 103°F. by rectum, and a steady, squeezing right-lower-quadrant pain developed. The abdomen was tender in the entire right lower quadrant and around the umbilicus. No spasm was found, but there was marked rebound tenderness referred to the

FIGURE 2. *Roentgenogram of the Abdomen, Taken Seven Weeks Later.*

A dilated loop of small bowel appears to outline the superior aspect of the mass in the lower portion of the abdomen slightly to the left of the midline.

right lower quadrant. Rectal examination revealed two very tender uterosacral ligaments. The glove stool specimen was faintly guaiac positive. On the next day, the white-cell count was 24,900. An anteroposterior x-ray film of the abdomen showed a loop of bowel overshadowing the lower lumbar spine and appearing to go around a mass of some sort, although this could have been fluid-filled loops of bowel in the area that created the illusion of an abnormal tumefaction (Fig. 2). The temperature had declined to 101°F. Maximal abdominal tenderness was present beneath the left rectus muscle, although there was still some tenderness on the right side. Later on the same day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. MARSHALL K. BARTLETT*: May we see the x-ray films?

DR. C. C. WANG: As stated in the protocol, in the

*Visiting surgeon, Massachusetts General Hospital.

pyelogram done on the second admission, one of the upper calyxes of the right kidney shows some irregularity and poor filling with contrast medium, suggesting some infectious process in this region. A gastrointestinal series on the day after the retrograde pyelogram reveals nothing unusual in the upper gastrointestinal tract or the intestines. There appears to be an extrinsic pressure defect on the barium-filled small bowel (Fig. 1), apparently from a large soft-tissue mass in the left lower quadrant, but the examination of the abdomen made on the previous day shows nothing so that I believe that the mass could conceivably represent a distended bladder. The film of the abdomen taken on the last examination again demonstrates a smooth soft-tissue mass in the mid-lower left side of the abdomen measuring approximately 10 cm. in greatest diameter (Fig. 2).

DR. BARTLETT: Would you show us the barium-enema examination?

DR. WANG: The barium-enema examination discloses nothing unusual — no intrinsic defects in the colon and a mucosal pattern that appears normal. There is some barium refluxing into the terminal ileum. There is no evidence of Meckel's diverticulum.

DR. BARTLETT: There is no evidence of a mass in the abdomen?

DR. WANG: I do not recognize a mass in the abdomen.

DR. BARTLETT: Dr. Wang has taken the wind out of my sails by belittling the mass to which I have given considerable thought. If he is correct, and no mass is present in the abdomen, some of the diagnoses that I shall consider could be ruled out.

This twelve-year-old girl was admitted three times, with pain and symptoms and signs that were subacute or subsided promptly after admission. During the third admission, after the symptoms had subsided, a more severe and somewhat different pattern of symptoms and signs developed and led to the operation. The variable shifting type of this pattern is interesting. Also of interest is the note at the time of the third admission that each typical attack ended abruptly, with some mild residual soreness. It seems to me that I shall have to consider the urinary, genital and gastrointestinal tracts to find an explanation for this problem.

Certainly, the left-flank pain at the time of the second admission makes one think of some process involving the urinary tract. The presence of 75 red cells per high-power field in the sediment at the time of the first admission also points that way. Several times it was noted that the pain was either brought on or aggravated by emptying the bladder, and there was urinary frequency and urgency. None of these were consistently present, some being present on one attack, and some on others. A cystoscopic examination revealed no disease in the bladder, and a retrograde pyelogram was certainly equivocal. The only abnormality that was noted was on the right side, and yet most of the symptoms, except in the last attack, were on the left side of the abdomen. Although the possibility must be considered, I doubt if this process will prove to be related to the urinary tract.

Was it related to the pelvic viscera? Ovarian cysts occur in this age group, although they are not common. A dermoid is the cyst most frequently seen in children. Some dermoids contain enough calcium to be visible in the x-ray films. There is no indication in the x-ray films that this mass, if there was a mass, was a dermoid. The only evidence for an ovarian cyst is the fact that a mass may have been present in the abdomen. Against that is the fact that at no time in these various examinations was this mass felt. A rectal examination was only recorded on two occasions and apparently was not satisfactory since the patient was not co-operative. Nevertheless, I think it is unlikely that an ovarian cyst of this size could not be felt. Such a cyst would not ordinarily cause blood in the gastrointestinal tract as evidenced by the strongly positive guaiac test on the last admission. I think the disease was not related to the genital tract.

Was there disease in the gastrointestinal tract? I shall have to start with the commonest of all causes of an acute abdominal process, appendicitis, but I do not think it fits the picture at all. Most of the symptoms were on the wrong side, although appendicitis can produce symptoms on the left side even in the presence of normal anatomy. It would not give an explanation for the mass unless an appendiceal abscess had developed, which I do not think would have given such intermittent symptoms. I shall also rule out mesenteric adenitis, which is another common cause of acute abdominal symptoms in a girl of this age, because it also leaves me without an explanation for the space-filling mass in the lower abdomen. The ++++ guaiac test certainly brings to mind the possibility of some kind of intussusception. The ordinary type of intussusception would be relatively rare in a girl as old as this. I think that is very unlikely.

There are various congenital conditions that I must mention. An omental cyst could provide a mass such as this, but the x-ray findings do not allow me to place this either posterior or anterior to the intestinal loops, which might give a clue. An omental cyst only rarely causes symptoms unless it becomes acutely twisted and its blood supply is impaired. It would be unlikely for an omental cyst to cause intermittent pain. Mesenteric cysts occur in the mesentery of the small bowel or of the colon, more commonly in the former, and may produce intermittent symptoms, which may eventually become acute enough to require intervention. This is the age group in which that condition is likely to cause trouble. The symptoms are thought to be due to kinking or twisting of the intestine, and perhaps that would account for the ++++ guaiac test on the last admission. It is difficult for me to explain the acute episode that led to the operation on the basis of a mesenteric cyst. The temperature spiked to 103°F., the white-cell count rose, and the abdominal signs increased greatly, ex-

tending down into the right lower quadrant, around the umbilicus and on the next day to the region of the left rectus muscle. Duplication of the intestine is difficult to distinguish from a mesenteric cyst, but such a duplication is likely to cause difficulty at an early age.

Meckel's diverticulum I shall consider more seriously than the others because, although it is apt to produce symptoms in early childhood, it may cause them at any age. A Meckel diverticulum produces symptoms in various ways. A band may extend between the tip of the diverticulum and the umbilicus and serve as a point for small-bowel obstruction. Ulcers may develop, with hemorrhage — that probably did not happen here because the bleeding was minimal. The diverticulum may become acutely inflamed and perforate, as an acutely inflamed appendix does. It may be a leading point of an intussusception. In that case I should have to assume that the intussusception was repeated and reduced itself, which is not very likely. It may also give trouble by means of torsion, with interference of the blood supply of the diverticulum, and with enlargement and the formation of a mass that may be difficult to feel. That is the best possibility in this case.

In conclusion, I think that this condition was based on a congenital abnormality, the most likely being a Meckel diverticulum, which would explain the shifting type of symptoms and the acute episode that led to operation.

DR. E. DENOVIAN: Would you consider regional enteritis?

DR. BARTLETT: The patient had almost nothing in the way of gastrointestinal symptoms or signs except the positive guaiac test. She had nausea and vomiting, with some of the attacks of pain, but had no change in bowel habits. The terminal ileum was well visualized in the barium-enema examination, which, however, was done four years before the last episode and was therefore, perhaps, not reliable. I do not see that I have much evidence on which to base that diagnosis.

DR. FARAHE MALOOF: How do you explain the 75 red cells per high-power field in the sediment?

DR. BARTLETT: They were not found in any subsequent examination. I am sure it was one of the things that led to the investigation of the urinary tract, but I cannot find any evidence to substantiate a process there.

DR. MALOOF: Can a Meckel diverticulum irritate the ureter and produce red cells in the urine?

DR. BARTLETT: I suppose any acute intestinal process can do it.

A PHYSICIAN: What significance do you think the cloudy discharge had?

DR. BARTLETT: I attach no significance to that because it was noted on only one occasion. Whether it was there at the time of the other examinations would be important to know, and since I do not know it, I cannot interpret that finding.

CLINICAL DIAGNOSIS

?Congenital intestinal or mesenteric anomaly.

DR. MARSHALL K. BARTLETT'S DIAGNOSIS

Congenital anomaly, ?Meckel's diverticulum.

ANATOMICAL DIAGNOSIS

Twisted dermoid cyst of ovary, with hemorrhagic infarction.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Dr. Quinby, would you tell us the opinion on the ward?

DR. WILLIAM C. QUINBY, JR.: My first reasonings ran absolutely parallel to Dr. Bartlett's with a similar conclusion, even after examination under anesthesia. If he had known that the x-ray film was taken twelve hours after the temperature rose to 103°F. and when the bladder was definitely empty it might have made a difference in the diagnosis. After we talked with the radiologists, we gave more credence to a space-occupying mass than the radiologist did today. Dr. Richard C. Tefft had followed the patient for six months and found no abnormality in the urine on many examinations.

DR. CASTLEMAN: Will you tell us about the ether examination?

DR. QUINBY: On the ward rectal examinations were most unsatisfactory since the patient resisted vigorously at all times and showed a reaction akin to panic whenever approached for this purpose. On the morning after the rise in temperature and increased symptoms we decided to examine her under anesthesia and proceed as required. We found a virginal introitus and a small cervix, which seemed to be developing and was in midposition. The uterus could not be definitely made out. On rectal examination I thought the cervix was definitely separate from an abdominal mass the size of a large orange, which was round and could be pressed into the pelvis from its position to the left of and below the umbilicus. One could feel the mass by pelvic examination far up at the finger tip. I could not identify the mass closely with the genital organs. I made a diagnosis of some peculiar mesenteric cyst or anomaly in relation to a Meckel diverticulum.

Operation disclosed a large cystic mass of a dermoid variety that had arisen in the left ovary and rotated through more than 360°. The uterus was quite small, and the "uterosacral ligaments" that the house officer identified the night before were apparently the adnexa and tube twisted around the anterior part of the base of the cyst. The left fallopian tube was very hemorrhagic, scarred and wound up in the mass. The cyst was removed; we waited, while doing an appendectomy, for the blood supply to the tube to manifest itself clearly, but it seemed to be precarious and it appeared best to remove the cyst.

I want to say that this whole picture was complicated by the conviction that the symptoms were on an emotional basis; because for months the child would suddenly become very ill, her mother would give her an aspirin, and an hour or two later she would be fine. When I originally saw her in Dr. William A. Dickson's office, I remembered that twice before I had seen children whose emotional patterns were such that initially I was perfectly certain that they were on a hysterical basis. On each occasion infarction of some abdominal organ was present. We admitted her to the hospital immediately. In retrospect it seems almost certain that an ovarian cyst had been intermittently twisting and enlarging. Her personality is now quite normal.

DR. BARTLETT: How do you account for the blood in the stool?

DR. QUINBY: The cyst must have been twisting and untwisting for some time. Although its base arose from the pelvis it had drawn the uterus upward when it became too large to fit into the pelvis easily. At operation it was wedged into the pelvic inlet, pressing firmly against the sigmoid. There was a certain amount of inflammation on the surface of the sigmoid. I believe that the infarction of the cyst wall in continuity with the sigmoid wall is what produced the blood.

DR. CASTLEMAN: Microscopically, this was a characteristic dermoid, with squamous cells, keratin and skin appendages. It was infarcted and contained hemorrhage throughout its wall.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

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MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

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ON OR ABOUT THANKSGIVING

THE *Journal's* tradition of publishing an editorial of thanksgiving on or about the day annually proclaimed for the purpose of expressing appreciation seems to go back some fifteen years. Thanksgiving had been celebrated previously but not apparently by the *Journal*, which appears to have refrained until then from any exhibition of the emotions and enthusiasms to which mankind is subject. At that time, when troops had begun to march and countermarch across the face of Europe, the venerable publication became suddenly conscious of the fact that there was still something to be thankful for; or, to avoid the final preposition, something for which to be thankful.

The custom, good or bad, has curiously persisted, so that each year, regardless of any signs of general world decay that may have manifested themselves, the editors have compulsively set about the recording of at least one or two developments for which gratitude might be expressed. The year now passing has been no exception.

A consideration of the current year leads naturally to the subject of weather, about which so much discussion has taken place and which has steadily worsened despite all efforts to improve it. A year of record rainfall and visitations from three hurricanes, yclept like virgin harpies, are not in themselves causes for rejoicing; gratitude from most of the population comes in having survived them. And if Miss Carson's calm assumption that a change of climate is already causing the polar icecaps to dissolve into the seven seas is correct, then some fraction of mankind will be thankful for a new ark, as generously receptive as the *Mayflower*, and a new Noah to skipper them to the new continent that is expected to rise where Greenland now lies depressed beneath its towering weight of snow and ice.

Obviously, it cannot be expected that everyone will be grateful for the same things, for incompatibilities continue to exist. The blessings of blue skies, the right amount of rain at the right time, an abundance of food and plenty of gasoline, with or without additives, can be generally appreciated. Republicans and Democrats cannot be expected to share the same satisfaction at the outcome of elections, though both can be grateful for the fact that elections are still held. As Franklin (Benjamin, not F. D. R.) intimated at the signing of the Constitution, "You have now a republic; try and keep it."

Members of all parties except the Communist, therefore, can be thankful for the basic fact of the recent bye-election, even if it meant good-bye to a number of hopeful aspirants. Perhaps also it helped to focus attention on the most important subject in American life today — the matter of civil liberties and the need for thanks each time they are preserved.

THE FALLING SICKNESS IN CHILDHOOD

EPILEPSY is a problem of prime importance to the pediatrician, since it has been estimated that over 90 per cent of convulsive disorders have their onset during the early years of life. Thom found that 1 child in 14 of nearly 3500 children under the care of the Community Health Association in Boston had had one or more convulsions. Many spells of various types, other than cryptogenic or secondary epilepsy, however, must be given consideration in differential diagnosis, particularly the forms due to intracranial infections, hemorrhage or tumor, renal disorders, the effect of convulsant drugs, lead encephalopathy, allergy, migraine and even behavior disturbances or narcolepsy. The causes are multiple, and much skill is needed to detect them. No convulsion in a child should ever be considered a minor form of illness, and the beginning of essential epilepsy must always be kept in mind.

The subject of epilepsy in childhood has recently been thoroughly reviewed by Samuel Livingston,* director of the Johns Hopkins Hospital Epilepsy Clinic, in a comprehensive and authoritative monograph. He studied over 4000 children and classified 53 per cent as having cryptogenic epilepsy. The most common time of onset was between four and eight years of age; over half the children had generalized seizures; 13.5 per cent had petit-mal, and less than 5 per cent had focal attacks. Electroencephalograms were abnormal in about 70 per cent; except in a few cases there was no definite relation between the clinical and the electroencephalographic pattern. There was little reason to subject these patients with epilepsy to pneumoencephalography — in a series of pneumoencephalograms in 82 patients who had focal seizures or focal abnormalities in their electroencephalograms, no demonstrable abnormalities were revealed in any case.

Of the secondary epilepsies, cerebral birth injuries were the most common cause, closely followed by congenital developmental diseases of the brain. Other causes were rarely found, and brain abscess, tumor and syphilis accounted for only 3 each in 1518 patients. Vascular lesions were by no means uncommon, particularly thromboses of the dural sinuses occurring during the later part of the first year and rarely after the age of three.

Although recurrent seizures are produced by the predisposing factor of spontaneous transient disturbances of nerve-cell function, the specific cause of which is not known, there are precipitating factors that deserve attention. Infection and fever often initiate epilepsy in young children, and disorders of menstruation, photic stimuli, excessive hydration, sleep and hyperventilation also precipitate attacks.

In recent years, although the electroencephalogram occupies an important place among the tests available for the diagnosis and localization of cerebral lesions causing epilepsy, the most striking changes have been in the drug treatment of the disease. Bromide therapy goes back a hundred years, to 1853, but modern treatment began with the introduction of phenobarbital in 1912, diphenylhydantoin sodium (Dilantin) in 1938 and a large number of other anticonvulsant drugs in subsequent years. In Livingston's series phenobarbital (or Mebaral) and Dilantin were most effective for major motor seizures in children, phenobarbital and the bromides for minor motor seizures, Benzedrine, Paradione or Tridione for petit-mal attacks, and Dilantin or Mesantoin for psychomotor seizures. But for children between two and five years of age, treatment by a ketogenic diet was given preference for both major and minor motor although not for petit-mal seizures. Of the drugs, the bromides and phenobarbital (or Mebaral) have the least untoward reactions. Mesantoin, Paradione, Tridione and Phenurone may affect the hematopoietic system, Dilantin may cause ataxia, diplopia, hyperplastic gums and hirsutism, and each of them may evoke cutaneous disturbances.

To the general practitioner and the pediatrician, therefore, a convulsion in a child is not to be dismissed as an innocuous incident. The various causes must be reviewed, and the results applied to the individual patient, the value of dietary and drug treatment weighed, the type of drug or the combination of drugs decided upon, and a continuity of care provided for. Most epileptic persons live with controlled attacks if continuously supervised; those who do badly are usually patients who "shop around" for physicians or for quick cures. Like diabetes, pernicious anemia and the deficiency diseases, epilepsy is best considered a long-time — perhaps a lifetime — disease, requiring persistent treatment, adjusted to changing conditions, over the years. Proper diagnosis, an artful balance of many forms of treatment and continuity of supervision are the three most important factors in successful management. In few other diseases is complete coordination between a personal medical adviser and the patient so important and advantageous.

*Livingston, S. *The Diagnosis and Treatment of Convulsive Disorders in Children.* 320 pp. Springfield, Illinois: Thomas, 1954.

NEW ENGLAND "NORTHER"

MATTERS that affect the safety of the public are of medical as well as general concern, and the epidemiology of accidents has become a practical problem in the teaching of public health. The road designer, then, may be considered an agent of preventive medicine, and the Boston to Worcester turnpike an unsavory example of the utter failure of his craft. On this stretch of roadway, now undergoing purely palliative treatment, corrective measures are long overdue; nor is the principal booby trap hard to locate. Some ten years ago, a Kentucky physician diagnosed the difficulty as resting primarily in the numerous foreshortened cutoffs that connect east-bound and westbound traffic lanes. "Down our way," he said, "we'd

call this a 'Norther'; it has all the earmarks of a superhighway but it ain't."

Despite the closing off of more than 75 dangerous intersections between east-bound and west-bound traffic lanes, Route 9 between Worcester and Boston remains a somewhat shoddy imitation of the real thing — presuming this to be the interpretation of the Kentucky colloquialism. A deadly speed trap for those who happen to drive on it for the first time, it is deceptive in the invitation it offers to cruise along at the supposedly safe rate of 45 or 50 miles an hour and the unexpected abruptness with which conditions change. For all the closing off of some crossovers, others have not been closed; they are now rendered more hazardous than ever since the flow of traffic has been generally smoothed out and speeded up.

The great difficulty is that the crossovers that remain are so cramped that a car turning from one lane to another is forced to wait with its rear end thrust out into the high speed lane from which it came until the opposite lane happens to be cleared of traffic — or until some combination of circumstances conspires to force a collision of an oncoming car into the waiting vehicle. The consequences are usually a lacerating series of blows or death for some unsuspecting visitor to Massachusetts, and perhaps a "whiplash" injury* of the neck sustained by occupants of the road-blocking car, which is more likely than not of local origin; all this because highway engineers of the gay 20's did not anticipate the need of leaving enough room for an automobile to creep into calm waters while waiting its chance to cross over.

Few members of today's driving public can remember when the last high-speed trolley made its run from Boston to Worcester, and fewer still remember when horse-drawn vehicles were regularly seen going to and from the farms along the countryside and when the horses gave way to automobiles of the vintage that now make Glidden tours each fall. Some of them had chain drives, some were steamers, and some were air cooled. At about this period the engineers took a hand in remaking the turnpike for posterity.

Trolley tracks were ripped up, and asphalt was put down in that wonderful pattern of the machine age — the two-lane highway. No longer was it necessary to pull a hay wagon almost into the ditch to pass a smart surrey setting out from Southborough for an all-day trip to Boston. But just in case the surrey or the hay wagon or a chain-driven Stutz bearcat wanted to swing over from the east-bound to the west-bound lane, intersections were left, large enough for two hay wagons to pass each other, but no larger. Why waste asphalt? And so, although the center strip had all the room potentially that would be needed for any car, no matter how fast it might be moving, to get in out of the high-speed lane on the left and wait for traffic in the opposite lane to clear, this room was never utilized, and many lives and much property were lost — and will continue to be lost until a reasonable elongation of existing crossovers is made.

Despite the fact that the curbing installed a few years ago along the center strip was finally laid back from the vertical at the cost of many thousands of dollars, despite the fact that over 70 unnecessary wagonways have been closed off and despite new surfacing and many new signs, the Worcester turnpike remains an antiquated "Norther" and a death trap for unwary adolescents, nearsighted adults and strangers from Kentucky.

*Gay, J. R., and Abbott, K. H. Common whiplash injuries of neck. *J.A.M.A.* 152:1698-1704, 1953.

NEW DEAN OF PUBLIC HEALTH

THE appointment of Dr. John C. Snyder as dean of the Harvard School of Public Health justifies the confidence in its future of those who have watched the University's venture in preventive medicine take shape in the twenties, develop in the thirties and come to maturity in the postwar period under the leadership of the late General James S. Simmons. However, the challenge that confronts the new dean is more than a matter of administration, money raising, faculty appointments and curriculum evaluation, and of holding the gains — and they were many — that were scored previously.

As public health moves ahead, its horizons, like those of its parent, medicine, enlarge to a concern with matters scarcely under consideration twenty-five years ago. The greater scope and possibilities of prevention affect the activity of the School and its graduates alike. The course ahead cannot be predicted, but both in teaching and in practice scientific methodology is certain to be applied to affairs involving the public health. The natural tendency to approach new problems only where they can be seen—and that belatedly and empirically—has been found costly and ineffective; society has haltingly learned the high value of scientific methodology in the prevention of diseases as well as in their cure. It augurs well for the Harvard School of Public Health that its new dean is a scientist first and an administrator second.

Dr. Snyder brings to his position a sound preparation in medicine and the mastery of a discipline, microbiology. Over and above his specific accomplishments he has demonstrated a knowledge of principle necessary in attacking successfully the unknown problems of the future, and when striking out in a new direction. He has made significant contributions both in the laboratory and in the field. His social conscience is implicit in his acceptance of the challenge to be dean at the cost of lifelong interests that he will have to curtail.

President Pusey in appointing a successor to General Simmons has selected one on whose judgment he can rely as Harvard seeks to develop a purposeful future for practice, teaching and research in public health. Beyond confidence and congratulations no more can now be said; the time is not ripe. Another able scien-

tist, Dr. Soma Weiss, once defined this kind of reservation in the aphorism: "In Hungary we have a saying: 'Praise the day after sunset.'" The inclusion of this quotation is no pompous caution to wait and see how well the new dean functions. Rather, it is the unvoiced feeling of millions throughout the world who look to the medical profession for help and advice in the days ahead — days when physicians themselves will ponder the implications of their inheritance, their present position in society and the validity of Descarte's pronouncement: "Si l'espèce humaine peut être perfectionnée, c'est dans la médecine qu'il faut en chercher les moyens."

Massachusetts Charitable Eye and Ear Infirmary. — *The daily newspapers furnish us with the intelligence, that a Report of the condition of this Institution, and its doings for the past year, has been published; but as we are not in receipt of a copy, we are unable to lay before our readers even a list of the present officers.*

Boston M. & S. J., *Nov. 29, 1854*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

GLICKMAN — Alfred M. Glickman, M.D., of Springfield, died on November 1. He was in his fifty-seventh year.

Dr. Glickman received his degree from Tufts College Medical School in 1921. He was a member of the New England Obstetrical and Gynecological Society, Association of Military Surgeons of the United States, Maimonides Medical Society, the staffs of the Springfield, Wesson Memorial and Wesson Maternity hospitals and legislative councilor from Hampden District in the Massachusetts Medical Society and a fellow of the American Medical Association, International Board of Surgeons, American College of Surgeons and the Springfield Academy of Medicine.

He is survived by his widow, son, sister and brother.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date	Clinic Consultant
Haverhill	December 1	William T. Green, M.D.
Greenfield	December 2	Charles L. Sturdevant, M.D.
Salem	December 6	Paul W. Hugenberger, M.D.
Gardner	December 7	Carter R. Rowe, M.D.
Brockton	December 9	George W. Van Gorder, M.D.
Lowell	December 10	Albert H. Brewster, M.D.
Worcester	December 10	John W. O'Meara, M.D.
Lynn*	December 13	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Pittsfield	December 15	Edward J. Coughlin, Jr., M.D.
Fall River	December 20	David S. Grice, M.D.
Springfield	December 21	James D. Fisher, M.D.
Hyannis	December 23	Paul L. Norton, M.D.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

Rheumatic-Fever Clinic	Dates
Fitchburg	December 1, 8, 15, 22, 29
North Reading	December 7, 14, 21, 28

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

CORRESPONDENCE

"SYMBOLIC EXPLANATIONS"

To the Editor: The editorial in the September 16 issue of the *Journal* entitled "Physiology of Anxiety" in praising the excellent article "Physiologic Psychology of Neurosis," by Altschule overlooks one most regrettable statement on the part of the author.

Enumerating ways in which emotions may affect bodily activity (page 479) the author says "Symbolic explanations belong in the realm of analogic magic and need not be discussed here." I wonder how many readers understand the meaning of such a cryptic expression and if the author himself realizes that the very words he uses to write the article are symbols. Does he, too, realize that the one activity in which man differs from the ape is in his capacity to communicate by written and spoken symbols? I interpret his reference to symbolic explanations as referring to the considerable body of psychoanalytic theory that has made and is continuing to make a significant contribution to the understanding of psychosomatic disorders. I know personally a number of internists and other nonpsychiatric specialists who are being trained in the art of psychotherapy based on these very "symbolic explanations." It would be indeed heartening to any physician to witness the satisfaction and pleasure with which these medical men see their formerly resistant patients respond to this new implement in their armamentarium.

I should like to point out, too, that the concealed name calling that the quotation implies causes the article to lack the scientific objectivity for which we are all striving. The hostility in the quotation, although not so sharp as a sword nor so lacerating as barbed wire, is there, a covert trace of the universal hostility and aggression that exists in all men and, because many of our finest intellects cannot accept its presence, has so far foiled our most strenuous efforts to bring peace to us all.

HERBERT I. HARRIS, M.D.

Cambridge, Massachusetts

Dr. Harris's letter was submitted to Dr. Altschule, who offers the following explanation:

To the Editor: Dr. Harris is correct in stating that all language is symbolic. This matter has been discussed extensively by semanticists and anthropologists in recent years; Cassirer, in fact, has said, "Instead of defining man as an *animal rationale*, we should define him as an *animal symbolicum*."

With respect to my choice of adjective, either "allegorical" or "metaphorical" would have been more appropriate, but I felt obliged to use "symbolic" in view of its special connotation in the psychiatric literature.

MARK D. ALTSCHULE, M.D.

Waverley, Massachusetts

PATHOGENESIS OF COGAN'S SYNDROME

To the Editor: The interesting case report, "Nonsyphilitic Interstitial Keratitis and Bilateral Deafness (Cogan's Syndrome) Associated with Essential Polyangitis (Periarteritis Nodosa)," by Oliner, Taubenhaus, Shapira and Leshin, which appeared in the *New England Journal of Medicine* (248:1001-1008, 1953), has only recently come to my attention. The authors report another case of this syndrome and consider a possible pathogenic mechanism. This carefully studied case provokes a great many worthwhile thoughts. In 1945 I was fortunate in seeing and reporting the sixth case of this syndrome *(Arch. Ophth.* 41:24-31, 1949). Although the authors state that I considered this reported case an atypical variety of postvaccinial encephalitis, it was primarily my aim to show the significance of the delayed or incubation period after the introduction of any virus and to stress the etiologic factor when symptoms appear at a specific interval after the vaccination. It is now generally accepted that all symptoms that appear ten to twelve days after vaccination are the result of the introduced "vaccinia." In subsequent reports I have tried to show that this specific and original report might be likened to a basic laboratory experiment, thus establishing a type of pattern reaction for many substances that call forth a bodily response whether they are introduced through the skin, nose, mouth or vein. The introduction of "vaccinia" virus acts as an example of how virus of any form (poliomyelitis, measles, mumps or influenza) works when acquired by the body. An incubation period occurs, and then a definite series of bodily reactions follow. I have tried to stress the importance of the incubation period and the onset of symptoms after exposure in relation to this incubation period.

The excellent and carefully documented report by Oliner and his associates is a noteworthy contribution to medical literature. Of its thoroughness and careful preparation there can be no doubt; nevertheless, many self-incriminations seem evident. There is at least a suspicion that the state of periarteritis nodosa is "physician induced," and this situation is becoming much more frequent in the present "antibiotic age." Does not this case present evidence of the production of the hypersensitive state through overuse of antibiotics in a patient apparently hypersensitive or in a state of reactivity? In a recent article in the *Journal of Pediatrics* (39:346-353, 1951) Adelson stated, "in closing it may be pointed out that the warning uttered by Rich that continued administration of a sulfonamide or of a foreign serum after symptoms of hypersensitivity have appeared, carries the danger of producing visceral damage of the periarteritis nodosa type." This applies equally to penicillin and must be kept in mind when allergic manifestations first make their appearance. It is quite possible that persons who manifest a state of sensitivity may be made hypersensitive through use of certain drugs.

The patient in the report of Oliner et al. was of allergic disposition to begin with, and may have had nothing more than a Ménière syndrome and a keratitis, both of which may be allergic conditions. Then, through the use of antibiotics and other substances, a state of hypersensitivity was induced so that when the third episode occurred the patient was prone to periarteritis nodosa. It is interesting that the authors quote the work of Rich *(Bull. Johns Hopkins Hosp.* 71:123, 1942), who is the proponent of the theory of the hypersensitive state induced by certain drugs, and yet that they fail to realize that they induced the same state of affairs in their own patient.

It would be interesting and enlightening to know on which side of the face the dental abscess was present and what was done for the abscessed tooth from the dental point of view.

Novocain, which frequently acts as a sensitizing agent, may have been of some importance in this case. The development of the maculopapular rash on the left side of the face during the third hospital admission leads me to suspect that the dental abscess was on the left side and that a local anesthetic was used for the dental infections.

It may be of some further interest to the authors to point out that in the second series of cases reported by Cogan *(Arch. Ophth.* 42:42-49, 1949) Case 2 developed a week after vaccination for smallpox. Although I do not wish to stress vaccination as the etiologic factor in this syndrome and have desired only to demonstrate that it represents a prototype to help understand the importance of symptoms setting in at a specific period of incubation, 2 of 16 cases appeared shortly after vaccination. Therefore, this is an etiologic factor of increased importance. In conclusion, although the authors believe that their case is unique in that after two episodes the clinical picture of periarteritis nodosa developed, it seems to me that any patient presenting the Cogan syndrome would be converted into this "unique picture" through the use of hypersensitizing drugs and that if these drugs are used in patients who are especially allergic, periarteritis nodosa will probably be induced much more frequently.

EMANUEL ROSEN, M.D.

Newark, New Jersey

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Confederate Surgeon's Letters to His Wife. By Spencer Glasgow Welch, surgeon, Thirteenth South Carolina Volunteers, McGowan's Brigade. 12°, cloth, 127 pp., with illustrations. Marietta, Georgia: Continental Book Company, 1954. $5.00. (New York and Washington: Neale Publishing Company, 1911.)

The letters of Dr. Welch cover the period from May 16, 1862, to May 2, 1865. They have been condensed by the elimination of uninteresting personal matter. The small book, a reissue of the original printing of 1911, is well published.

After the Doctor Leaves: A practical guide to approved post-medical care and treatment of chronic diseases for the patient and his family. By Marguerite Clark. With a foreword by Howard A. Rusk, M.D. 8°, cloth, 310 pp. New York: Crown Publishers, Incorporated, 1954. $3.75.

Marguerite Clark, who has been the medical editor of *Newsweek* for a number of years, has written a book for the laity on the care of persons afflicted with chronic diseases. The chapters deal with heart disease, high blood pressure, rheumatism and arthritis, cancer, diabetes, ulcers, tuberculosis, allergies, diseases of the central nervous and musculoskeletal systems and mental and emotional troubles. The final chapter concerns old age. The author was assisted by a large number of physicians and specialists.

The Meaning of Social Medicine. By Iago Galdston, M.D., secretary, Medical Information Bureau, New York Academy of Medicine. 8°, cloth, 137 pp. Cambridge, Massachusetts: Harvard University Press, 1954. $2.75. (Published for the Commonwealth Fund.)

The author discusses various aspects of social medicine, its present status and the "failure" of modern medicine; etiologic medicine; the "epidemic constitution" — influenza and the great pandemic of 1918 and 1919; mortality and morbidity; social medicine and medical education. There is an appendix on social medicine in England. A bibliography is appended, and there is a good index. The book should be in all collections on the subject.

The Atom Story: Being the story of the atom and the human race. By J. G. Feinberg, M.Sc., with illustrations by Lewis and a foreword by Frederick Soddy, F.R.S. 8°, cloth, 243 pp., with illustrations. New York: Philosophical Library, 1953. $4.75.

The author tells an interesting story of the atom beginning in the fifth century, B.C., with Anaxagoras and Democritus. A valuable appendix deals with survival under atomic attack. There are a glossary of terms and a good index.

Handbook of Cardiology for Nurses: Heart disease and its treatment: the patient and his nursing care. By Walter Modell, M.D., F.A.C.P., assistant professor, Cornell University Medical College, assistant professor, Cornell University-New York Hospital School of Nursing, chief, Children's Cardiac Clinic and Adolescent Cardiac Clinic, Beth Israel Hospital; and Doris R. Schwartz, B.S., R.N., instructor, Cornell University-New York Hospital School of Nursing, supervisor of nursing, Comprehensive Care and Teaching Program, New York Hospital-Cornell Medical Center. Foreword by Edna L. Fritz, R.N., National League for Nursing. Second edition. 8°, cloth, 320 pp. New York: Springer Publishing Company, Incorporated, 1954. $4.25.

The first edition of this book was published in 1952, and the need of a second issue in 1954 indicates its acceptance by the nursing profession. No mention is made of a revision of the text. There is a good index, and the book is well published.

Preservation and Transplantation of Normal Tissues. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.; and Margaret P. Cameron, M.A., A.B.L.S. Assisted by Joan Etherington. 8°, cloth, 236 pp., with 55 illustrations. Boston: Little, Brown and Company, 1954. $6.00. (*A Ciba Foundation Symposium.*)

Seventeen papers were read and discussed at this symposium, held in London during March, 1953. Short lists of references are appended to the articles, and the publishing is good. The series should be in all medical libraries.

Seventy-Five Years of Medical Progress 1878-1953. Edited and with a foreword by Louis H. Bauer, M.D., F.A.C.P., secretary-general, World Medical Association. 8°, cloth, 286 pp., with illustrations. Philadelphia: Lea and Febiger, 1954. $4.00.

In April, 1953, the first Western Hemisphere Conference of the World Medical Association was held in Richmond, Virginia. Representatives of nineteen medical specialties (as defined by the Advisory Board of Medical Specialties) and one of general practice read papers on the progress and present status of each specialty. The publishing is good, but the lack of an index is noted. The volume should be in all medical libraries.

Illustrated Review of Fracture Treatment. By Frederick Lee Liebolt, M.D., Sc.D., LL.D., attending surgeon in charge of orthopedics, New York Hospital, attending orthopedic surgeon, Hospital for Special Surgery, and associate professor of clinical surgery (orthopedics), Cornell University Medical College. 4°, paper, 229 pp., with 605 figures. Los Altos, California: Lange Medical Publications, 1954. $4.00.

This semi-atlas, designed for the medical student, house officer and the general practitioner, illustrates and discusses the principal features concerning diagnosis and treatment. There are 605 figures and a good index.

Laboratory Instruments: Their design and application. By A. Elliott, Ph.D., D.Sc., Courtaulds Limited; and J. Home Dickson, M.Sc., Royal Naval Scientific Service. 8°, cloth, 414 pp., with illustrations. New York: Chemical Publishing Co., Incorporated, 1953. $7.50.

The authors have presented the fundamentals of the construction of scientific instruments for laboratory use. One hundred and forty-two pages are devoted to glass, lenses, mirrors and prisms and optical instruments. The publishing is excellent, and an index is included. The book is a valuable reference source for interested persons, including opticians and refractionists.

Pediatric Problems in Clinical Practice: Special medical and psychological aspects. Edited by H. Michal-Smith, Ph.D., chief clinical psychologist, Flower and Fifth Avenue Hospitals, and research associate in pediatrics, New York Medical College, with 14 contributors. 8°, cloth, 310 pp., with illustrations. New York: Grune and Stratton, 1954. $5.50.

The various types of sick children are discussed by 13 authorities in their particular fields. After a discussion of the normal and sick child the chapters deal with the emotionally disturbed, schizophrenic and mentally retarded child, as well as the child with brain injury and cerebral palsy and those who are orthopedically handicapped, allergic, diabetic, epileptic and tuberculous. Each of the chapters has a list of references, and there is a bibliography of recommended readings for parents. There is a good index. The book should be in pediatric and neurologic collections.

Newer Concepts of the Causes and Treatment of Diabetes Mellitus. Proceedings of the symposium on diabetes sponsored by the New York Diabetes Association and held at Memorial Hospital and the New York Academy of Sciences, New York City, October 8, 1953. 8°, paper, 181 pp., with illustrations. New York: National Vitamin Foundation, Incorporated, 1954. $2.50.

Thirteen papers were read and discussed at this symposium, including 3 on various aspects of experimental diabetes, the action of insulin, control of complications, indications for the use of various insulins, management during pregnancy, effects of life situations and the emotions on treatment, the management of surgical infections, with special reference to streptokinase-streptodornase, and nutritional therapy.

The Biochemistry of Clinical Medicine. By William S. Hoffman, Ph.D., M.D., professorial lecturer in medicine, University of Illinois College of Medicine. 8°, cloth, 681 pp., with illustrations. Chicago: Year Book Publishers, Incorporated, 1954. $12.00.

This new book has been written especially for the general practitioner without special training in chemistry and physiology. The early chapters, which discuss the biochemical subjects, are followed by those of a clinical character. Lists of references are appended to the chapters, and there is a good index.

Geriatric Medicine: Medical care of later maturity. Edited by Edward J. Stieglitz, M.S., M.D., F.A.C.P., consulting internist, Suburban Hospital, Bethesda, Maryland, and Washington Home for Incurables, chairman of staff, 1945-47, Suburban Hospital, Bethesda, Maryland, consultant in geriatrics, Chestnut Lodge, Rockville, Maryland, St. Elizabeths Hospital and Veterans Administration, associate, Washington School of Psychiatry, lecturer in industrial medicine, New York University-Bellevue Post-Graduate Medical School, chairman, Advisory Council on Professional Education, Commission on Chronic Illness, and consulting editor, *Geriatrics.* Third edition. 4°, cloth, 718 pp., with 205 illustrations. Philadelphia: J. B. Lippincott Company, 1954. $15.00.

This new edition of an authoritative book, first issued in 1943, is the joint work of 48 contributors. The text has been extensively revised and brought up to date. The sections deal with basic considerations, disorders of metabolism, the mind and the nervous system and the various systems of the body. There are 42 chapters, to which lists of references are appended, and there is a comprehensive index. The book is recommended for all collections on the subject.

Diseases of the Liver. By Mitchell A. Spellberg, M.D., F.A.C.P., associate professor of clinical medicine, University of Illinois School of Medicine, and associate attending physician, Department of Medicine, Michael Reese Hospital, Chicago, Illinois. 4°, cloth, 646 pp., with 93 illustrations, 77 tables. New York: Grune and Stratton, 1954. $16.50.

Dr. Spellberg has reviewed and evaluated the modern knowledge of the liver and its diseases, intentionally omitting historical and old writings. The text is divided into 12 sections on clinical laboratory tests of hepatic function, needle biopsy, differential diagnosis of jaundice, neoplasms and cysts, toxic hepatitis, infections, diet in liver disease,

anatomy of the liver and its vascular supply and diseases resulting from disturbances in the major vessels, cirrhosis, the role of the endocrine glands in liver disease, and hepatorenal relation, the liver in other diseases and liver disease associated with inborn errors of metabolism. There is a bibliography of over 2400 references and a good index; the publishing and illustrative work are excellent. This valuable reference book should be in all medical libraries.

Peripheral Circulation in Man. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Jessie S. Freeman, M.B., B.S., D.P.H. Assisted by Joan Etherington. 8°, cloth, 219 pp., with 72 illustrations. Boston: Little, Brown and Company, 1954. $6.00. (*A Ciba Foundation Symposium.*)

This symposium is complementary to an earlier one on visceral circulation. Thirty-two persons took part in reading and discussing the various papers covering the methods for studying blood flow, the changes in circulation caused by exposure to cold or heat, the action of epinephrine and norepinephrine on blood flow, the significance of cold agglutinins and the influence of visceral activity on the peripheral circulation.

First Aid and Resuscitation. by Lieutenant Carl B. Young, Jr., M.P.H., instructor, Emergency First Aid, first lieutenant, Medical Service Corps, U.S.A.R. 8°, cloth, 338 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $8.50.

Lieutenant Young describes emergency procedures for rescue squads, firemen, policemen, ambulance crews, interns and industrial nurses. The author stresses the necessity of taking complete charge of the patient at the scene of the operation and the obligation of giving aid during transportation to a physician or hospital. All possible emergencies are covered. The material is well organized, and the manual should prove valuable to those persons for whom it is written.

Theory and Problems of Adolescent Development. By David P. Ausubel, M.D., Ph.D., Bureau of Educational Research, University of Illinois. 8°, cloth, 580 pp., with illustrations. New York: Grune and Stratton, 1954. $10.00.

The author presents his material in four parts, as follows: introduction, in which the subject is discussed in general; psychobiologic problems; psychosocial problems; and maladjustment and mental hygiene. There are 17 chapters, to which lists of references are appended. The modern literature is surveyed throughout the text, and there are indexes of authors and subjects. The book should be of interest to pediatricians and psychiatrists.

The History of the Medical Department of the United States Navy in World War II. A Narrative and Pictorial Volume. Edited by Bennett F. Avery, Captain (MC) USN. Volume 1. 4°, paper, 380 pp., with 172 illustrations and 36 tables. Washington, D.C.: United States Government Printing Office, 1953.

This condensed history covers the medical services with the various expeditionary forces, air evacuation, aviation and the specialties. There are special chapters on the program for the deaf, blindness, medical research, clinical psychology in the screening program, medical aspects of blast, rehabilitation and malnutrition in repatriated prisoners of war. The volume should be in all collections on medical history and military and naval medicine.

Anoxia of the New-born Infant: A symposium organized by the Council for International Organizations of Medical Sciences. Consulting editors, Dr. Kenneth W. Cross (United Kingdom), Dr. Marcel Lelong (France) and Dr. Clement A. Smith (United States); editors for the Council, J. F. Delafresnaye, C.I.O.M.S., Paris, France, and T. E. Oppé, St. Mary's Hospital, London, England. 8°, cloth, 230 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1953. $5.50.

The participants in this conference came from various countries of Europe, with the exception of one from the United States, Dr. Clement A. Smith, of Boston. The material is arranged in four sections on clinical, histologic and pathological, biochemical and physiopathological considerations. This type of book should be in all medical libraries.

A Manual of Tropical Medicine. By Thomas T. Mackie, M.D., colonel, M.C., A.U.S. (retired), chairman, American Foundation for Tropical Medicine, and consultant in tropical medicine, Roosevelt Hospital, New York City, Veterans Administration Hospital, West Haven, and Norwalk Hospital, Norwalk, Connecticut; George W. Hunter, III, Ph.D., Colonel, M.S.C., U.S.A., chief, Section of Parasitology-Entomology, Fourth Army Medical Laboratory, Brooke Army Medical Center, Fort Sam Houston, Texas, professor of parasitology, Affiliated Units of the Graduate School, Baylor University; and C. Brooke Worth, M.D., field staff member, Division of Medicine and Public Health, Rockefeller Foundation. Second edition. 8°, cloth, 907 pp., with 304 illustrations, 7 in color. Philadelphia: W. B. Saunders Company, 1954. $12.00.

The first edition of this book was published in 1945 during World War II. This new edition has been revised and brought up to date with the assistance of 24 collaborators. The publishing is excellent, and the book will be a valuable addition to medical libraries and collections on the subject.

NONCLINICAL NOTES

HEMOPHILIA FOUNDATION

The national office of the Hemophilia Foundation announces the establishment of a national Medical Advisory Council to guide the Foundation in its scientific program. The members of the Council are as follows: Drs. Benjamin Alexander, Kenneth M. Brinkhous, John H. Lawrence, Armand J. Quick, Leandro M. Tocantins, Louis R. Wasserman and Maxwell M. Wintrobe. Dr. Martin C. Rosenthal has been appointed medical secretary of the Foundation.

NOTICES

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston, on December 8, from 11:00 a.m. to 5:00 p.m. and at the Longwood Towers, Brookline, from 5:30 p.m. (refreshments and dinner). The program is as follows:

Grand Rounds, Children's Medical Center. Dr. Charles A. Janeway and staff.

Clinicopathological Conference. Dr. Sidney Farber.

Scientific Session. Dr. James M. Baty, presiding.

Incidence and Spread of Illnesses in Families. Dr. John Dingle.

Members are invited to submit abstracts of papers.

NEW YORK SOCIETY FOR CIRCULATORY DISEASES

A meeting of the New York Society for Circulatory Diseases will be held in Room 440 of the New York Academy of Medicine on Tuesday, December 14, at 8:30 p.m. The topic of the meeting will be "Graphic Methods in Congenital and Rheumatic Heart Disease." Dr. Samuel O. Sapin will speak on the subject "Analysis of the Electrocardiogram and Vectorcardiogram in Congenital Heart Disease," and Dr. Alvin J. Gordon on the topic "Left Atrial Pulmonary Capillary and Esophageal Balloon Pressure Pulses in Mitral-Valve Disease." All physicians are invited.

NEW YORK ACADEMY OF MEDICINE EASTERN STATES HEALTH-EDUCATION CONFERENCE

The Eastern States Health-Education Conference of the New York Academy of Medicine will be held at the Academy, 2 East 103d Street, New York City, April 21 and 22, 1955.

NATIONAL RESEARCH COUNCIL GRANTS

The Division of Medical Sciences, National Academy of Sciences, National Research Council, is accepting applications for grants-in-aid of research in three fields as follows:

Research in the physiologic, biochemical and pharmacologic effects of alcohol supported by the Committee on Problems of Alcohol. Applications should be received before January 15, 1955.

Research on the mechanisms controlling sexual behavior in animals and man, involving endocrinologic, neurologic, psychologic, anthropologic, phylogenetic and genetic studies and the physiology of reproduction and related biologic and biochemical fields, supported by the Committee for Research in Problems in Sex. Applications should be received before February 15, 1955.

Research in the fields of analgesia and addiction and information on basic research being conducted in these fields in order to act as a center for the exchange of information, supported by the Committee on Drug Addiction and Narcotics.

Further information and application blanks may be obtained from the appropriate committee of the Division of Medical Sciences, National Academy of Sciences — National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D. C.

POSTGRADUATE COURSE IN OCCUPATIONAL MEDICINE

A series of eight lectures and discussions on the general topic "Occupational Medicine for General Practitioners," sponsored by the Section of Occupational Health, Department of Public Health, Yale University School of Medicine and the Committee on Industrial Health of the Connecticut State Medical Society and providing sixteen hours of postgraduate training for the American Academy of General Practice, will be given at the staff room, Bridgeport Hospital at 8:30 p.m. as follows:

December 3. Workman's Compensation.
January 7. Nonoccupational Illness: Cardiac, diabetic, tuberculous.
January 28. Psychiatric Problems in Workers.
February 11. Occupational Diseases.
February 25. Administration of Health Programs.
March 11. Insurance Programs, Certification of Illness.
March 25. Occupational Skin Disease; Diagnosis.

The meetings are open to all interested physicians.

SOCIETY MEETINGS AND CONFERENCES

November, 1954–April, 1955. Postgraduate Medical Institute. Page 451, issue of September 9.
November, 1954–May, 1955. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.
November 29–December 1. Association of Military Surgeons of the United States. Page 631, issue of October 7.
November 30, 7:00 p.m. House Officers' Association. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
December 1. New England Conference on Allergy. Page 875, issue of November 18.
December 1, February 4 and April 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of October 14.
December 3. New England Society of Anesthesiologists. Page 876, issue of November 18.
December 3. New England Rheumatism Society. Page 875, issue of November 18.
December 3, 1954–March 25, 1955. Postgraduate Course in Occupational Medicine. Notice above.
December 4–9. American Academy of Dermatology and Syphilology. Page 876, issue of November 18.
December 4, 1954–May 7, 1955. Middlesex South District Medical Society, Postgraduate Course. Page 758, issue of October 28.
December 5. American Academy of Dental Medicine. Page 1092, issue of June 24.
December 6, 1954–January 17, 1955. Hartford Medical Society. Page 496, issue of September 16.
December 7. Medical Television Program.. The Doctor. (Cavalcade of America.) Page 631, issue of October 7.
December 8. New England Pediatric Society. Page 921.
December 8. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.
December 8 and 9. Myasthenia Gravis Foundation Conference. Page 834, issue of November 11.
December 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.
December 14. New York Society for Circulatory Diseases. Page 921.
January 3–May 9, 1955. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.
January 10–15. Course in Care of Atomic Casualties. Page 285, issue of August 12.
February 4 and April 1, 1955. New England Society of Anesthesiologists. Page 1054, issue of June 17.
February 7–9. McIntyre-Saranac Conference. Page 410, issue of September 2.
February 11–25. Pan-American Academy of General Practice. Page 496, issue of September 16.
March 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.
March 22–26. International Academy of Proctology. Page 876, issue of November 18.
April 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Notice above.
May 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.
June 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.
June 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, DECEMBER 2

THURSDAY, DECEMBER 2

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45-9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building. Children's Medical Center, 35 Binney Street.
*9:00-10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00-10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00-11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Thoracic Conference. The Embryologic Basis of Congenital Heart Defects. (New and Old Films.) Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.-12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.-1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:00 m.-1:00 p.m. Some Histochemical Observations on the Origin of the Primordial Germ Cell in the Human Embryo. Dr. Arthur T. Hertig. Stearns Auditorium, New England Center Hospital.
*4:00-5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

FRIDAY, DECEMBER 3

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30-11:30 a.m. Medical and Surgical Grand Rounds, Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Clinical Conference. Uterine Inertia. Dr. E. Devlin. St. Margaret's Hospital, Dorchester.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00 p.m. New England Society of Anesthesiologists. Hotel Beaconsfield, Brookline.
*4:00-5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
8:00 p.m. New England Rheumatism Society. Rheumatologic Aspects of Bone Disease. Dr. I. Snapper. Sherman Auditorium, Beth Israel Hospital.

SATURDAY, DECEMBER 4

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00-9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

(Concluded on page xxi)